(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 March 2002 (28.03.2002)

PCT

(10) International Publication Number
WO 02/24264 A1

(51) International Patent Classification[7]: A61M 15/00

(21) International Application Number: PCT/SE01/01942

(22) International Filing Date:
12 September 2001 (12.09.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0003364-7 21 September 2000 (21.09.2000) SE

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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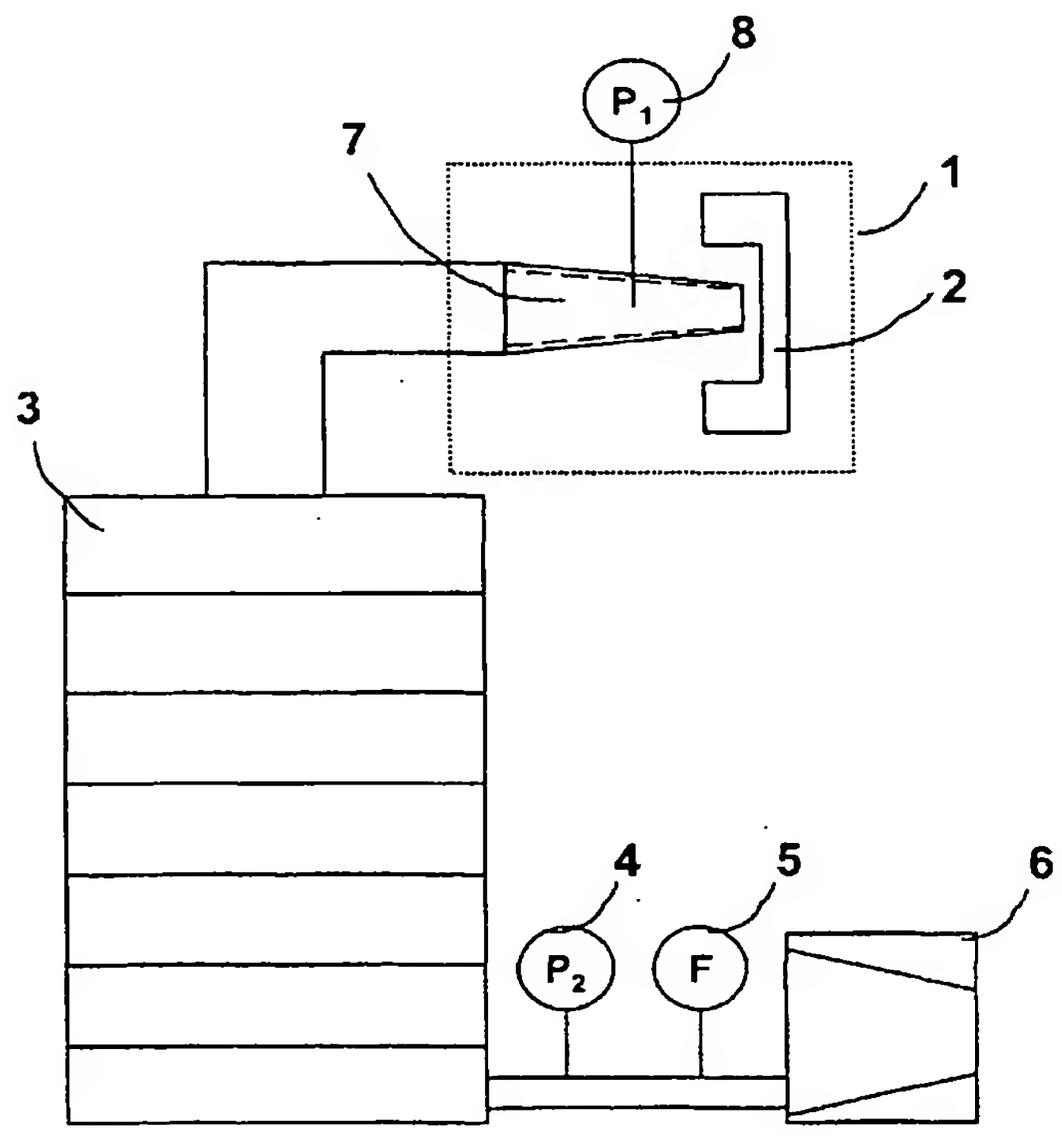
(54) Title: OPTIMIZATION OF AN ELECTROSTATICALLY DOSED DRY POWDER INHALER



(57) Abstract: A method and a process are disclosed for optimizing an electrostatically dosed dry powder inhaler (EDPI) for utilization of a prepared pre-metered electro-dose consisting of an electro-powder. An arrangement is set-up for measuring parameters affecting a systemic delivery or local lung delivery of a pre-metered electro-dose from a DPI including analysis of dose de-agglomeration, particle size distribution as well as dose-to-dose variation together wit pressures times and flows. A dry powder inhaler, DPI, is adjusted for a system or a local lung setting with respect to activation pressure and closing pressure having a DPI with a 20 to 60 liters per minute inhalation air flow for systemic delivery setting and 20 to 80 liters per minute for a local lung setting. Furthermore the de-agglomeration power is adjusted between 0.1 and 6 watts to be used in the DPI by optimizing the pressure drop and inhalation flow rate by changes to the mouthpiece and/or the device member and their relation to each other. The DPI activation pressure is further adjusted to a value between 0.5 and 4kPa to eliminate the low power at the start of the inhalation. The method and process then verify that the DPI meets the specifications set regarding de-agglomeration of powder and opening and closing pressures together with timings within the DPI active time. Furthermore is verified that de-agglomeration difference, expressed in percent using an expression 100[1-de-agglomeration($_{Q1kPa}$)/de-agglomeration(Q)], is not more than 50%. Finally if the DPI is not approved as an EDPI the tested DPI and/or electro-dose is further adjusted to check if the DPI can meet the specifications of an EDPI.

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Declaration under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Optimization of an electrostatically dosed dry powder inhaler

TECHNICAL FIELD

The present invention relates to administration of medication powders into the respiratory tract by releasing an electrostatically dosed powder to be inhaled and more particularly to a method for optimizing the function of an electrostatically dosed dry powder inhaler (EDPI) in relation to a pre-metered dose of electro-powder.

BACKGROUND

Dosing of drugs is carried out in a number of different ways in the medical service today. Within health care more and more is focused on the possibility of dosing medical drugs as a powder directly to the airways and lungs of a user by means of an inhaler in order to obtain an effective, quick and user-friendly administration of such substances. But today the dosing quality is not good enough to be used for a wide range of drugs. This is specially the case for systemic delivery by inhalation through a dry powder inhaler (DPI) which represents an important segment making it possible to compete with the injection needle for many types of drugs, i.e. insulin, pain management etc.

A dry powder inhaler of today, represents a device intended for administration of powder into the deep or upper lung airways by oral inhalation. With deep lung should be understood the peripheral lung and alveoli, where direct transport of active substance to the blood can take place. Particle sizes, to reach into the deep lung, should be in a range 0.5 - 3 μm and for a local lung delivery in the range 3 - 5 μm. A larger grain size will easily stick in the mouth and throat, and a smaller grain size may accompany the expiration air out again.

To succeed with systemic delivery of medication powders to the deep lung by inhalation there are some criteria, which have to be fulfilled. The most important is a very high degree of de-agglomeration of the medication

powder but also an exact dose is of great importance. This is difficult with dry powder inhalers of today without special arrangements as for example a so called spacer. By means of a spacer the small grains are evenly distributed in a container from which the inhalation can take place. Upon inhalation from the spacer the fine powder is floating free in the air and will effectively reach the alveoli's of the lung. This method in principle has two drawbacks, firstly difficulties to control the amount of medicine emitted to the lung as an uncontrolled amount of powder sticks to the walls of the spacer and secondly difficulties in handling the relatively space demanding apparatus.

It is also common to utilize carriers i.e. lactose having a larger grain size onto which the fine power is distributed. Upon inspiration the large size grains will then stick in the oral cavity while the fine particle fraction, this is powder smaller than 5 μm, will be let free and proceed to the lung. For instance U.S. Patent No. 5,642,727 discloses a tribo-inhaler having a container portion for electrostatically retaining a predefined dose of medicament powder. The container portion contains a plurality of polymeric beads that have diameters of approximately 50 to 200 microns. Each of the polymeric beads has a specific quantity of dry powder medicament electrostatically adhered to its surface.

A U.S. Patent No. 5,871,010 addresses an inhaler apparatus with modified surfaces for enhanced release of dry powders. The inhaler apparatus disclosed comprises interior surfaces having low surface energy for minimizing contact between a medicament and the surfaces of the inhaler to minimize deposition of the dry powder.

Powders for inhalers have a tendency of agglomerating, in other word to clod or to form smaller or larger lumps, which then have to be de-agglomerated. De-agglomeration is defined as breaking up agglomerated powder by introducing electrical, mechanical, or aerodynamic energy. Sometimes de-

agglomeration is performed as a stage one during dosing and as a final stage two during the user's inspiration through the DPI.

Inhaler devices normally use the force exerted by the user's more or less normal inspiration effort for de-agglomerating the medication substance administered when inhaling in an effort to bring as much as possible of the active substance into the lungs. This often leads to inhaler designs using high pressure drops, which will put the user's lungpower to the test.

Technologies to de-agglomerate today include advanced mechanical and aerodynamic systems and combinations between electrical and mechanical filling systems that can be seen in for instance in U.S. Patent No. 5,826,633. Further there are systems disclosed for dispersing aerosolized doses of medicaments, e.g. U.S. Patent No. 5,775,320, U.S. Patent No. 5,785,049, and U.S. Patent No. 5,740,794. Furthermore, in our International Publications WO 00/0636 and WO 00/6235 principles for de-agglomeration and classification are disclosed.

To meet some of the demands an electrostatic dosing of the powder onto a technical means for example a cassette can be done. An electrostatic dosing onto a device member or cassette was described in our Swedish Patent No. 9802648-7 (SE512 433) and the quality can be improved by utilizing the possibility to classify coarse particles larger than 5 μm to leave those out and dose only fine particles (less than 5 μm) onto the device member or cassette as described in our Swedish Patent No. 9802649-5 (SE512 386).

The term "electrostatic dosing" is used throughout this document as a generic term describing methods of forming a dose of finely divided dry powder by electrically charging the powder particles and applying electrostatic techniques or controlled electric field techniques or a combination of these techniques to transport, distribute and deposit the charged particles onto a selected target area of a substrate with full control of relevant dose parameters, like total mass and space geometry. After

forming of the dose, the dose charge may remain, naturally decay over time or be actively neutralized by some means depending on what type of administration system the dose is supposed to be used in.

The term electro-powder rcfers to a micronized medication powder presenting controlled electrostatic properties to be suitable for electrostatic administration in an inhaler device. Such an electro-powder provides possibilities for a better dosing from electrostatically operating equipment such as disclosed in our U.S. Patent No. 6,089,227 as well as our Swedish Patents No. 9802648-7 and 9802649-5, which present excellent inhalation dosing performance.

One major problem is to obtain a low relative standard deviation (RSD) between doses with this type of technique due to lack of in line control possibilities in production making it hard to be in compliance with regulatory demands. For metered doses of medication substances the relative standard deviation between doses (RSD) should preferably be not more than <5 %. For DPIs of prior art the fine particle fraction and uniformity of dose together with the user dependency is a major drawback and this can be seen from: "A Critical Comparison of the Dose Delivery Characteristics of Four Alternative Inhalation Devices Delivering Salbutamol: Pressurized Metered Dose Inhaler", Diskus Inhaler, Diskhaler Inhaler, and Turbuhaler Inhaler", Journal of Aerosol Medicine, volume 12, Number 2, 1999, Mary Ann Liebert, Inc., pp 75-84.

Often, devices of prior art technology do not reach a sufficiently high degree of de-agglomeration and an exact dose is not well developed and leaves much to be desired when it comes to dosage conformity and lung deposition effectiveness of the medication substance.

This means there is still a demand for a dry powder inhaler where the important functions have been optimized to give a very high de-agglomeration meaning a high fraction of particles under 5 μm for local lung

and under 3 μm for deep lung and a uniformity of dose that is independent of minor variations in the users inhalation.

SUMMARY

A method and a process are disclosed for optimizing an electrostatically dosed dry powder inhaler (EDPI) for utilization of a prepared pre-metered electro-dose consisting of an electro-powder. An arrangement is set-up for measuring parameters affecting a systemic delivery or local lung delivery of a pre-metered electro-dose from a DPI including analysis of dose de-agglomeration, particle size distribution as well as dose-to-dose variation together with pressures times and flows. A dry powder inhaler, DPI, is adjusted for a systemic or a local lung setting with respect to activation pressure and closing pressure having a DPI with a 20 to 60 liters/minute inhalation air flow for systemic delivery setting and 40 to 80 liters/minute for a local lung setting. Furthermore the de-agglomeration power is adjusted between 0.1 and 6 watts to be used in the DPI by optimizing the pressure drop and inhalation flow rate by e.g. changes to the mouthpiece and/or the device member and their relation to each other. The DPI activation pressure is further adjusted to a value between 0.5 and 4 kPa and optionally a closing pressure between 0.5 and 4 kPa to eliminate the low power at the start and end of the inhalation. The method and process then verify that the DPI meets the set specification regarding de-agglomeration power and opening and closing pressures together with timings inside the active time of the DPI, and that the de-agglomeration generates at least 50% fine particle fraction by weight measured according to USP as the fraction below 5 μm. Furthermore is verified that de-agglomeration difference, expressed in percent using an expression 100[1- de-agglomeration(Q_{1kPa})/de-agglomeration(Q)], is not more than 50%. Finally if the DPI is not approved as an EDPI the tested DPI and/or electro-dose is further adjusted to check if the DPI can meet the specification of an EDPI.

A method according to the present invention is set forth by the independent claims 1 and 15 and the dependent claims 2 to 14, and 16 to, 19.

Furthermore a process for obtaining an EDPI is set forth by the independent claims 20 and 24, and further embodiments of the process are set forth by the dependent claims 21 to 23, and 25 to 37.

SHORT DESCRIPTION OF THE DRAWINGS

The invention, together with further objects and advantages thereof, may best be understood by making reference to the following description taken together with the accompanying drawings, in which:

FIG. 1 shows a measurement set-up used for a measurement of size distribution and mass and further calculation of de-agglomeration and flow rate;

FIG. 2 is a summary flow chart illustrating preparation of the DPI for obtaining an electrostatically dosed dry powder inhaler, EDPI;

FIG. 3 is a summary flow chart illustrating preparation of the DPI;

FIG. 4 is a summary flow chart illustrating a first analysis 1;

FIG. 5 is a summary flow chart illustrating a second analysis 2;

FIG. 6 illustrates the degree of de-agglomeration versus power in watts for an electro-dose;

FIG. 7 illustrates the inhalation power in watts versus time in seconds;

FIG. 8 illustrates the active time and the activation and closing for a deep lung setting and a local lung setting of the DPI with respect to the inhalation flow rate in liters/minute and the time in seconds;

FIG. 9 illustrates the inhalation volume in % of the total inhalation with respect to activation and closing for a deep lung or a local lung setting together with a safety margin of the DPI;

FIG. 10 illustrates the comfort area for an inhalation through a DPI as a mean over a population measured as inhalation flow rate in liters per minute versus pressure drop in kPa;

FIG. 11 illustrates the power levels compared with the comfort area of inhalation in accordance with FIG. 10;

FIG. 12 illustrates two device members with layouts for systemic delivery or local lung delivery of the electro-dose with respect to time in seconds;

FIG 13 illustrates a first example of an aerodynamically optimized mouth-piece together with an electro-dose on a device member;

FIG. 14 illustrates a second example of an aerodynamically optimized mouthpiece together with an electro-dose on a device member;

FIG. 15 illustrates a connection between a user and the DPI through a dissipative or conductive mouthpiece;

FIG. 16 is graph representing two different inhalations together with activation and closing of the DPI with respect to inhalation airflow in liters/minute and time in seconds;

FIG. 17 is a graph representing calculation of de-agglomeration for particles up to 3 micrometers from an initial electro-powder particle size;

FIG. 18 is a graph representing calculation of de-agglomeration for particles up to 5 micrometers from an initial electro-powder particle size;

FIG. 19 is a graph showing the amount of de-agglomeration at 5 μm (DD5μm) at different pressure drops measured as kPa over the DPI;

FIG. 20 is a graph showing the amount of de-agglomeration at 3 μm (DD3μm) at different pressure drops measured as kPa over the DPI; and

FIG. 21 is a graph showing the amount retention in the DPI at different pressure drops over the DPI measured as % of the pre-metered dose.

DESCRIPTION

An EDPI is a DPI optimized for local or systemic delivery of a metered electro-dose of 1μg to 10 mg of an electro-powder and presenting a dose de-agglomeration DD5μm and DD3μm (defined as percent by mass of de-agglomerated electro-dose powder particles less than 5 μm in aerodynamic diameter, $DD_{5\mu m}$, and 3 μm, $DD_{3\mu m}$, respectively) of more than 25 % together with a de-agglomeration difference measured according to USP compared with the de-agglomeration at a flow representing a pressure drop over the inhaler device reduced to 1 kPa (1 - (de-agglomeration(Q_{1kPa})/de-agglomeration(Q)) × 100) < 50 % and more preferably less than 25 % and most preferably less than 10 % and conform to the uniformity of dose stipulated in the USP. The uniformity of dose mass is expected to be between 90 and 110 % and preferable between 95 % and 105 %. By USP is referred to USP 24-NF 19 Supplement 601 Aerosols/Physical Tests, pages 2674-2688. USP is used throughout this document for reference to identify well-known methods of measuring relevant parameters, but other methods or regulatory criteria may be used by a person of ordinary skill in the art, without

departing from the spirit and scope of the invention as defined in the appended claims.

The EDPI can be a single or multi-dose EDPI with or without electrical assistance for the operation. The DPI activation at a set inhalation prcssure can be established by mechanical valves or by, e.g., an electrical sensor for sound or pressure and the closing of operation by a computer controlled timer or by a mechanical end point detection.

Particularly important is user independent particle size distribution and uniformity of dose. Measurements of these two properties are illustrated in an example of a de-agglomeration and mass measurement set-up in Figure 1, where the DPI **1** to be optimized is used to determine the particle size distribution and mass from a pre-metered electro-dose sucked up from the device member **2** through a mouthpiece **7** using an Andersen Impactor **3** to determine the aerodynamic particle size distribution. The total pressure drop over the de-agglomeration set-up is measured with a pressure gauge **4** and the flow-rate of the air is measured with a flow-meter **5** in liters/minute. Suction may be achieved by means of a pumping device **6** including components to control flow and pressure.

All measurements of the particle size distribution are measured at two different pressure drops at least over the inhaler device. All measurements are performed according to USP and then the pressure is changed for the measurement at a lower pressure 1kPa over the inhaler device **1** in point **8**.

The complementary particle size distribution is also measured at 1kPa pressure drop over the DPI **1** indicated by the pressure gauge **8** as differential pressure to the atmosphere and then the obtained flow-rate is noted down and named Q_{1kPa}. The particle size distribution obtained at the flow-rate Q_{1kPa} is then compared with the particle size distribution obtained at the flow rate Q_a meaning the flow rate obtained by using all other settings according to the USP.

The results of the de-agglomeration tests at two different pressures over the inhaler device and compared according to Figures 17 and 18 to determine if the results meets the specification for an EDPI and also if the de-agglomeration for 3 and 5 μm, DD3μm and DD5μm are within the specifications for the intended application EDPI and medical drug.

The DD3μm is used to optimise the EDPI for systemic delivery and the DD5μm is used for optimising for local lung delivery when this reflects the quality of the de-agglomeration in the particle size range important for the local and deep lung delivery of the electro-power.

A metered electro-dose is here defined as a dose formed from an electro-powder constituting at least one active powder substance or a dry powder medication formulation, which is metered onto a device member forming a dose carrier, a metered dose having a fine particle fraction (FPF) presenting of the order 50 % or more of its mass with a particle size between 0.5-5 μm, the dose further presenting an optimized porosity of 75 to 99.9 %. Porosity is defined as $Dp_{electro\text{-}dose} = 100 - 100(density_{electro\text{-}dose}/density_{electro\text{-}powder})$. $Density_{electro\text{-}powder}$ is defined as the density of the solid substance.

The electro-powder is defined as a medication powder intended for electrostatic dosing, formed of an active powder substance or dry powder medication formulation having a fine particle fraction (FPF) with 50 % or more by mass of particles between 0.5 - 5 μm and providing electrical specification measured at room temperature with an absolute specific charge of the order of 0.1 to 25 μC/g (0.1×10^{-6} – 25×10^{-6} Coulomb/gram of negative or positive charge) and desired to present a charge decay constant Q_{50} of > 0.1 sec, where Q_{50} is defined as the time until 50% of the electrostatic charge is discharged, (for instance after a corona charging in an Electrical Low Pressure Impactor (ELPI) model 3935 from DEKATI LTD) and having a tap density of less than 0.8 g/ml and a water activity a_w of less than 0.5. Water activity a_w is a dimensionless quantity, which may, for instance, be

measured with an AquaLab model series 3 TE. Tap density is, for instance, measured by using a Dual Autotap from Quantachrome© Corporation according to British Pharmacopoeia for Apparent Volume method. Both water activity and tap density are quantities well know to a person skilled in the field of chemistry analysis.

Particles intended for the deep lung, here defined as the peripheral lung and alveoli, where direct transport of an active substance to the blood can take place, should have a particle size in the range 0.5 - 3 μm. For treatment in the local lung, defined as upper parts of the lung, where treatment normally takes place for instance in asthma treatment, the particle size should be in the range 3-5 μm. All particle sizes are defined as the size of the particles measured with for instance a laser diffraction instrument e.g. a Malvern Mastersizer for physical size classification or an Andersen Impactor for an aerodynamic size classification and if not stated otherwise always referred to as aerodynamic particle size and measured according to USP.

A powder having a very fine particle fraction (FPF) must be prepared as it is generally only particles between 0.5 and 3 μm that will be medically active by being transported to the deep lung. For local lung treatments by inhalation the particle size should be between 3 –5 μm.

A correct dose and a low dose-to-dose relative standard deviation (RSD) must be released from the inhaler. For electrostatically dosed dry powders with electrostatic properties inside set specification the relative standard deviation between doses (RSD) will not be more than 5 %.

Many active substances will be of interest to use for local lung delivery or systemic delivery. The active substance is generally a pharmaceutical active chemical or biological substance intended for administration into the deep or upper lung airways by oral inhalation from the DPI.

Optimization of the intended DPI starts in step **100** of Figure 2 by defining a device intended for delivering a de-agglomerated electro-dose consisting of an electro-powder into the deep lung for systemic delivery or delivery to the upper lung airways for local lung treatments. The process is advanced into step **110** for preparation of the DPI. The step **110** for preparation of the DPI further illustrated in Figure 3 is then started with adjustment of a proper activation pressure in a step **210**. The activation pressure step **210** is determined after considering Figure 6 showing the amount of de-agglomeration **10** in % at different power levels measured in watts according to Figures 17 and 18 where the electro-dose being loaded into the DPI is defined as an electrostatically dosed electro-powder possessing the following specification: Porosity defined as $Dp_{electro\text{-}dose}$= 100 – 100($density_{electro\text{-}dose}$/ $density_{electro\text{-}powder}$) > 75 % and having an optimized de-agglomeration of > 25 %, and preferably being more than 50 % and most preferably more than 75 % and meeting a dosage uniformity according to USP 24-NF 19 Supplement 601 Aerosols/Physical Tests pages 2674 - 2688 and Guidance for Industry Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation and Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics and times measured with a calibrated chronograph, which will hereafter be referred to as USP, and also possessing a de-agglomeration difference measured according to USP compared with the de-agglomeration at a flow representing a pressure drop over the inhaler device reduced to 1 kPa 100×(1 - (de-agglomeration(Q_{1kPa})/de-agglomeration(Q)) < 50 % and more preferably less than 25 % and most preferably less than 10 %.

In Figure 6 the area **I** indicates an energy level enough for a controlled de-agglomeration of the electro-dose when the difference over a wide range of energy is giving a high degree of de-agglomeration. If the energy level for the operation of the DPI is chosen to be within the area **II** a more uncontrolled de-agglomeration will occur and careful consideration must be made if this is a correct design of the DPI. Area **III** shows when the energy level of the de-

agglomeration test is not enough and the result is very unpredictable showing a very big difference from a small difference in inhalation power.

The activation pressure at step **210** should then normally be set within Figure 6 area **I** or **II** to have a safe design specification for the combination of electro-dose and DPI setting. Activation pressure at step **210** is measured using a pressure gauge to determine at what inhalation pressure normally between 1 and 4 kPa the DPI starts to be active, i.e. when the intended DPI in step **100** is going from a ready to a stage when the electro-dose is starting to be de-agglomerated into the mouthpiece and inhaled.

When the activation pressure in step **210** has been set the inhalation pressure and flow of step **220** is adjusted to obtain the correct power for de-agglomeration, according to Figure 6, during the inhalation through the DPI. When setting the inhalation pressure and flow at step **220** it must be realized that the power during the inhalation is achieved as a function of the inhalation airflow and the pressure drop.

The pressure drop of the DPI is the total pressure drop over the DPI and the major pressure drop within the DPI comes from the de-agglomeration of the electro dose in a relation $\Delta P_{de\text{-}agglomeration}/\Delta P_{total} \times 100 > 50$ %. This can be done by optimizing the aerodynamic construction of the mouthpiece and the device member and reducing the overall pressure drop inside the DPI .The mouthpiece should also be aerodynamically optimized to reduce retention of powder and electrically connected by a dissipative material to the user to eliminate electrical fields that will increase the retention in the mouthpiece.

If the DPI is set for an airflow between 40 and 60 liters/minute the pressure drop could be lower than if the inhalation airflow set for a deep lung delivery with 20 to 40 liters/minute and having the same effect regarding electro-dose de-agglomeration during the dose-delivery time, time(s) or time(a) for deep lung and local lung respectively.

After the setting of the inhalation pressure and flow at step **220** follows adjustment and setting of the dose delivery time in step **230** as this is of great importance for deciding delivery to the local lung or the deep lung. The dose delivery time of step **230** should be adjusted to take advantage of the power curve in an inhalation and make use of the highest power levels and cut off the beginning and end where much less de-agglomeration of the electro-dose will take place. In area I and II in Figure 6 the de-agglomeration of the electro-dose will have the best possibility to meet a specification set for an EDPI.

To achieve a deep lung delivery it is recommended that the inhalation airflow is between 20 and 40 liters per minute. High flows are to be avoided since amount of impaction in the upper airways is proportional to the particle speed and the square of the particle size. An ideal design specification for a deep lung setting of the DPI is a flow 20 to 40 liters per minute and a pressure drop between 1 and 2 kPa to avoid constricting the airways making them smaller and by this increasing the velocity of the air in the airways.

Looking at Figure 8, a normal inhalation **15** is described with an activation of the DPI with the inhalation flow rate **20** corresponding to an activation pressure and showing a deep lung setting **24** of the DPI compared with a setting **26** for local lung. Both the settings for deep lung and local lung have the same closing pressure **22**. The dose delivery time in step **230** is then set as t_s to T_s for a deep lung setting and from t_a to T_a for a local lung setting of the DPI with an activation pressure setting at t and a closing pressure at T, where the total dosing time for the deep lung setting is time(s)= $T_s - t_s$ and the time for local lung setting is time(a) = $T_a - t_a$ inside the total activation time for the DPI time = T – t.

When setting the dose delivery time at step **230** consideration must be made regarding the total amount of electro-powder that is going to be inhaled not to get too high concentration of powder and ensure a distribution of the powder over the active time. Distributing the electro-dose de-agglomeration

over the whole inhalation period is very favorable as this results in that as much as possible of the energy in the inhalation is utilized for de-agglomeration of the electro-dose. An aspect for the dose delivery time in step **230** is also a consideration of the depth of the delivery of the electro-dose into the lung and the amount of air needed for this transport down to the deep lung or the local lung. For local lung delivery normally 0.5 to 2 liters of air is needed but for deep lung delivery 2 to 3 liters is necessary due to the size of the lung and the air volume within the airways. An ideal design specification for the dose delivery time step **230** is for a deep lung delivery from t to t + 1.5 seconds, and for a local lung delivery setting from t+1 to t+1.75 seconds, but possible to adjust within the total activation time t to T for the DPI if necessary to ensure an optimized result. Looking at Figure 9 showing the total inhalation volume **15** of air it is shown that the total inhalation time should not be more than corresponding to 75 % of the user's total inhalation volume **15**. Area **33** in Figure 9 illustrates the amount of air volume necessary to transport powder from the inhaler to the local lung and the volume of air in area **32** illustrates the necessary air volume needed to transport powder from the DPI to the deep lung. The activation of the DPI if set for deep lung delivery is at **35** and ending at **37** giving a total dose delivery time time(s)= $T_s - t_s$. For a local lung setting of the DPI the DPI is activated for dose delivery at **36** and ending at **38** giving a total dose delivery time time(a) = $T_a - t_a$. Area **30** represents the variation within the population and serves as a safety margin to always have a setting of the DPI total time shorter than a user's inhalation time DPI time = T – t where also DPI time is less than the time for a user's inhalation.

Having set the dose delivery time at step **230** a next adjustment for the DPI is to set the closing pressure in step **240**.The closing pressure at step **240** secures and closes the DPI and is normally set to the same value as the activation pressure at step **210** or lower.

The physical adjustment of the DPI is now set and the DPI is ready for an analysis 1 at step **120** to determine if the prepared DPI meets the specification for an approved DPI at step **130**.

If the prepared DPI meets the specification set the process is transferred to step **140** for a prepared DPI. If the specification set is not met the process is transferred back via a step **135** to step **110** for preparation of the DPI by further adjustments.

The DPI prepared at step **140** is set for further tests together with an electro-dose in step **150** and for further tests in step **160** and a second analysis 2 in step **170** to determine if the prepared DPI at step **140** together with the electro-dose at step **150** meets specification set for an EDPI approval at step **190**.

The prepared DPI at step **140** is loaded with a metered electro-dose at step **150** and tested in step **160** according to USP. The prepared DPI is further taken into the second analysis 2 at step **170** measuring inhalation pressure and flow in step **220** together with dose delivery time in step **230** and dose de-agglomeration in step **430**.

In optimizing the properties of a DPI, de-agglomeration of electro-powder and electro-dose is very important. The de-agglomeration of electro-powder to prepare an electro-dose is defined as de-agglomeration #1 and de-agglomeration of electro-dose by inhalation is defined as de-agglomeration #2.

De-agglomeration #2 is measured at two different airflow values, whereby the first airflow Q is according to USP and the second airflow Q_{1kPa} is at a pressure drop over the inhaler device of 1 kPa. The two different airflow values determine if an increase in inhalation energy has a major effect on the de-agglomeration #2. It is important to minimize the effect of the inhalation energy by adjusting the de-agglomeration #2, the dosing properties and de-agglomeration #1 to meet the EDPI specification.

De-agglomeration #2 is measured using the prepared DPI of step **140**.

The de-agglomeration is then calculated using the electro-powder particle size specification as input material and the High Performance Liquid Chromatography HPLC analysis regarding particle size distribution after a standard sucking off powder from the device member as the output result. The de-agglomeration of the electro-dose is then calculated as percent of de-agglomerated electro-dose at 3 μm, DD3μm, and 5 μm, DD5μm, compared to the amount of powder less than 3 μm and 5 μm in the original electro-powder.

Figures 17 and 18 present calculations of de-agglomeration at 3 μm and 5 μm, respectively, in a graphical representation marking the areas under the particle size distribution curves for the initial and resulting distributions respectively. The curves plotted with dots representing initial electro-powder size distribution and the curves plotted with squares representing resulting size distribution from the mouthpiece.

Figure 17 describes how the de-agglomeration at 3 μm is calculated using the initially input electro-powder under 3 μm represented by the hatched area as a base. The amount of de-agglomerated powder from the electro-dose is then represented by the dark area under the curve showing resulting powder. By dividing the calculated value of the surface of the second area with the calculated value of the surface of the first area and multiplying by a factor 100 the de-agglomerated amount below 3 μm is obtained in percent referred to as DD3μm.

Figure 18 describes how the de-agglomeration at 5 μm is calculated using the initially input electro-powder below 5 μm represented by the hatched area as a base. The dark area under the curve showing resulting powder represents the amount of de-agglomerated electro-powder from the electro-

dose. By dividing the calculated value of the surface of the second area with the calculated value of the surface of the first area in Figure 18 and multiplying by a factor 100 the de-agglomerated amount below 5 μm is obtained in percent referred to as DD5μm.

The prepared DPI at step **140** will meet the specification for an EDPI if the electro-dose de-agglomeration analysis at step **430** shows a de-agglomeration difference measured according to USP compared with the de-agglomeration at a flow representing a pressure drop over the inhaler device reduced to 1 kPa (1 - (de-agglomeration(Q_{1kPa}) / de-agglomeration(Q)) × 100) < 50 % and preferably less than 25 % and most preferably less than 10 % referred to as ΔDD3μm and ΔDD5μm for deep lung and local lung DPI analysis of de-agglomeration difference.

This correlation is also best understood by looking at Figure 19 showing the de-agglomeration 5 μm in % for DPI A **85** and for DPI B **86** where DPI A shows a higher degree of de-agglomeration at higher pressure drops over the DPI properly because that the inhaler DPI A is having higher flow and therefore also a bigger power for de-agglomeration of the electro-dose. The velocity in DPI A is dropping quicker and at medium to low pressure drops the DPI A **85** is showing less de-agglomeration than the DPI B **86**.

The dose mass step **440** is measured to determine the uniformity of dose according to USP by chemical analyzes, e.g. a HPLC SpectraSYSTEM with a UV 6000 detector or any other suitable detector. A second option and also most preferable is to determine the powder mass using an Andersen Impactor and analyze both the aerodynamic particle size distribution and the total mass using for instance the HPLC SpectraSYSTEM in accordance with USP.

The dose retention at step **450** is defined as the unwanted amount of remaining electro-powder in the prepared DPI of step **140** after an inhalation or test at step **160** has been performed. Figure 21 shows how the amount of

retention **88** in % is changed when the pressure drop over the DPI is changed. The setting of the DPI to have an optimally prepared DPI at step **140** is important to minimize the retention and improve uniformity of dose. A low pressure drop **I** will have a higher retention due to less power in the inhalation and a too high pressure drop **III** will show more turbulence and by this more electro-powder will stick in the mouthpiece.

A data analysis in step **460** is performed and resulting in graphs according to Figures 6 to 9, Figures 11 to 12, and Figures 16 to 20. All graphs are analyzed to determine if the prepared DPI meets the specification set for an EDPI or is subject to optimization by going back via step **182** to preparation of DPI or the electro-dose needs to be optimized by going back via step **184** to electro-dose step **150**.

Figure 10 shows how different users experience the inhalation pressure versus the inhalation flow rate and the comfort area **40** represents the area where the users have a comfortable inhalation through the DPI. Normally the pressure drop must be below 4 kPa and the flow rate between 20 and 80 liters/minute.

Figure 11 shows the comfort area **40** inside a graph showing tests with three (3) different DPI settings I, II, III and power levels 42 A to H. The power levels are between 0.1 to 6 watts and inhalation flow rates 20 to 80 liters/minute and pressure drop over the DPI between 0.5 and 4 kPa. The graph will show how to best prepare the DPI with respect to inhalation comfort of the user.

Figure 12 shows a layout of two (2) different device members of electro-doses. Electro-dose **50** represents a deep lung setting between t_s and T_s with a de-agglomeration direction **54**. Electro-dose **55** represents a local lung setting between t_a and T_a also with a direction of de-agglomeration **54** and where T represents the total activation time of the DPI. The device member **52** can be made out of isolative, dissipative or conductive polymers characterized in that electro-conductive material used for the device member

is obtained from materials such as silver powder, platinum powder, gold powder, stainless steal powder, antimony-doped tin oxide, antimony-doped silica oxide, or is a X-doped silica where X is an adamantine semiconductor, e.g., Ge, ZnO, GaSb or an octahedral semiconductor, e.g. SnSe, AgSbSe2, InSb or carbon or any other electro-conductive material approved by FDA and possible to incorporate into plastics. And also that the conductive material and the plastic material for a dissipative or conductive combination of the device member and other dissipative parts in the EDPI has a specification presenting a surface resistance of 10^3 - 10^{12} Ω, and a volume resistivity of 10^3 - 10^{12} ohm·m.

Figure 13 shows an illustrative example of an aerodynamically optimized set-up of a mouthpiece **60** made up of a diffuser **62** and a nozzle **64**. The device member **52** together with the electro-dose **65** positioned to have an optimized transport through the mouthpiece into the user without any extra de-agglomeration assistance e.g. mesh. This construction will minimize the retention in the mouthpiece. The mouthpiece **60** can also be made in an electrically dissipative material to create an electrical contact between the user and the DPI to eliminate the possibility for uncontrolled electric fields that can increase unwanted retention of powder in the mouthpiece.

Figure 14 shows an illustrative example of a mouthpiece **60** and a diffuser **62** where the electro-dose **65** is blown off the device member **52** by high velocity air coming through tubes **66**. The blown off powder from the electro-dose is cleared from the active walls **67** by having 10 to 75 % of the inhalation air coming thorough the active walls **67**.

Figure 15 shows in an illustrative example a connection between the EDPI **72** having a conductive or dissipative mouthpiece and where the connection between a user **70** and an EDPI **72** is through the lips with a contact resistance **78**.The charge of the user is represented by the capacitance **76** and the user **70** electric charge is drained thorough a resistor **74**. By having a dissipative material in contact with the lips of the user, the EDPI and the

user **70** will have the same potential and no electrical fields disturbing the electro-powder will be present.

The description above will be better understood when looking at two theoretical examples whereby example 1 is for a local lung deposition and example 2 is for a systemic delivery of powder.

Example 1

Two different settings of the intended DPI at step **100** suited for an electro-dose in step **150** using Terbutaline sulphate (TBS) 100 µg for local lung delivery are prepared according to the following specification.

The specification for the DPI has been determined by looking at Figure 6 achieved from preparing and then analyzing the electro-dose. Figure 6 indicates de-agglomeration of the electro-dose of TBS as a function of power in watts..

The general setting for a local lung delivery is to have 60 liters/minute inhalation flow and from this it is possible from Figure 6 to calculate a pressure drop over the DPI that will give a de-agglomeration within set specification for an EDPI of TBS.

The above settings are possible to achieve by adjusting different dimensions inside the DPI. Figure 13 is showing an illustrative example of a mouthpiece with an electro-dose situated right under the opening. In this design it is possible to e.g. change the distance between the device member **52** and the nozzle **64** to introduce a higher resistance, alter the size of the mouthpiece **60** or reduce the middle section **62** to have different aerodynamic properties.

Figure 14 shows a second illustrative embodiment where different settings of the DPI are possible by changing nozzles **66** or distances or mouthpiece **60** together with the middle section **62**.

The aim of the settings for the DPI is to obtain an inhaler that will be as little as possible dependent on the inhalation path of the user and will give the best de-agglomeration of the electro-dose of TBS measured as DD5μm inside the comfort region **40** according to Figures 10 and 11.

DPI A

Inhalation flow	60	liters/minute
Inhalation pressure	2	kPa
Activation pressure	1.5	kPa
Dose delivery time t_a	1	s
Dose delivery time T_a	1.8	s
Activation time DPI T – t	3.0	s
Closing pressure	1.5	kPa
Electrical connection		yes

DPI B

Inhalation flow	60	liters/minute
Inhalation pressure	3	kPa
Activation pressure	1.5	kPa
Dose delivery time t_a	1	s
Dose delivery time T_a	1.8	s
Activation time DPI T – t	3.0	s
Closing pressure	1.5	kPa
Electrical connection		yes

These parameters are identified as the most suitable for a TBS electro-dose after analyzing Figure 6 where the most suitable inhalation power in watts is determined for the TBS electro-dose at step **150**. The activation pressure step **210** is set with respect to Figure 7 where the optimum effect in the inhalation is in region **I**, where the inhalation power is also at a maximum and the de-agglomeration of the electro-dose will be at an optimum. The point in time when the activation pressure is reached is at $t = t_s$ according to Figure 8 and at activation flow rate **20**.

After the preparation of the DPI at step **110** the respective inhaler is set to analysis 1 step **120** to determine if the settings are according to intended specification. All measurements are made according to USP and a set-up according to Figure 1 is used to measure the uniformity of dose and the dose de-agglomeration DD5μm.

All pressures are measured in the same way as the pressure drop over the DPI **8** as described in USP together using a chronograph to measure the time spans during the DPI activation time in step **250**.

Results from analysis 1 in step **120**

DPI A			
Inhalation flow	60	liters/minute	OK
Inhalation pressure	2.1	kPa	OK
Activation pressure	1.4	kPa	OK
Dose delivery time ta	0.9	s	OK
Dose delivery time Ta	1.6	s	OK
Activation time DPI T – t	2.8	s	OK
Closing pressure	1.5	kPa	OK
Electrical connection	yes		OK
DPI B			
Inhalation flow	60	liters/minute	OK
Inhalation pressure	3.2	kPa	OK
Activation pressure	1.4	kPa	OK
Dose delivery time ta	1	s	OK
Dose delivery time Ta	1.8	s	OK
Activation time DPI T – t	2.9	s	OK
Closing pressure	1.5	kPa	OK
Electrical connection	yes		OK

Analysis 1 at step **120** shows an approved result and both DPI A and DPI B are approved for further test and meet in step **140** the requirements for the prepared DPI.

An electro-dose of step **150** with TBS is now introduced and is inserted into the DPI for further tests at step **160**.

A set of tests at different pressures according to Figure 19 are defined and performed where the de-agglomeration is measured and the point where the de-agglomeration is changing drastically as in transition region **II** and region **III** with the pressure identified. Analysis is performed in accordance with USP and in a set up according to Figure 1 and measured using a HPLC.

As can be seen in Figure 19 the DPI A shows a worse behavior in region **II** compared with DPI B. If possible with respect to user comfort region **40** according to Figure 10 and behavior inside the comfort area according to Figure 11 the DPI B presents a safer setting but the DPI A has a higher performance inside region **I**.

Pressure drop kPa	De-agglomeration DD5µm %		Retention %	
	DPI A	DPI B	DPI A	DPI B
0.5	17	35	6.5	6
1	31	54	6	5
1.5	40	57	5	5
2	55	66	5	4
2.5	68	68	4	4
3	76	68	5	4
3.5	78	69	7	5
4	82	70	7	6

Regarding dose retention 88 Figure 21 shows the need to optimize the DPI to be used into region **II**.

A report for determining approved Y/N of step **180** is prepared to present the results of analysis 2.

Results from analysis 2

DPI A			
Inhalation flow	60	liters/minute	OK
Inhalation pressure	2.1	kPa	OK
Activation pressure	1.4	kPa	OK
Dose delivery time ta	0.9	s	OK
Dose delivery time Ta	1.6	s	OK
Activation time DPI T – t	2.8	s	OK
Closing pressure	1.5	kPa	OK
Electrical connection	yes		OK
DD5µm	55	%	OK
Retention	5	%	OK
DPI B			
Inhalation flow	60	liters/minute	OK
Inhalation pressure	3.2	kPa	OK
Activation pressure	1.4	kPa	OK
Dose delivery time ta	1	s	OK
Dose delivery time Ta	1.8	s	OK
Activation time DPI T – t	2.9	s	OK
Closing pressure	1.5	kPa	OK
Electrical connection	yes		OK
DD5µm	75	%	OK
Retention	5	%	OK

To verify if the DPI conforms to the specification of an EDPI the following calculations must be made.

	EDPI	DPI A	DPI B
DD5µm	> 25 %	55 %	68 %
Dose	2 µg - 10 mg	100 µg	100 µg
ΔDD5µm	< 50 %	62 %	23 %
Uniformity of dose	according to USP	Approved	Approved

DPI B shows an approved result in step **180** for the optimization and is suitable for local lung deposition of TBS as an EDPI loaded with an electro-dose of TBS. DPI A shows a high ΔDD5µm of 62 % and is not approved as an EDPI for TBS as this indicates that the DPI A is not independent of the user's inhalation pattern. DPI A is considered for further optimization at the DPI step **182** and/or an optimization of the electro-dose of TBS at step **184**.

Example 2

Two different settings of the intended DPI at step **100** suited for an electro-dose in step **150** using Insulin (INS) 800 µg for deep lung delivery are prepared according to the following specification.

The specification for the DPI has been determined by looking at Figure 6 achieved from preparing and then analyzing of the electro-dose. Figure 6 indicates de-agglomeration of the electro-dose of INS as a function of power in watts.

The general setting for a deep lung delivery is to have 40 liters/minute inhalation flow and from this it is possible from Figure 6 to calculate a pressure drop over the DPI that will give a de-agglomeration within set specification for an EDPI of INS.

DPI A

Inhalation flow	40	liters/minute
Inhalation pressure	1.5	kPa
Activation pressure	1.0	kPa
Dose delivery time ts	0.5	s
Dose delivery time Ts	2.0	s
Activation time DPI T – t	3.0	s
Closing pressure	1.0	kPa
Electrical connection	yes	

DPI B

Inhalation flow	40	liters/minute
Inhalation pressure	2.5	kPa
Activation pressure	1.0	kPa
Dose delivery time t_s	0.5	s
Dose delivery time T_s	2.0	s
Activation time DPI T – t	3.0	s
Closing pressure	1.0	kPa
Electrical connection	yes	

The aim of the settings for the DPI is to have an inhaler that is as little as possible dependent on the inhalation pattern of the user and gives the best de-agglomeration of the electro-dose of INS measured as DD3μm inside the comfort region **40** according to Figures 10 and 11.

These parameters are identified as the most suitable for an INS electro-dose after analyzing Figure 6 where the most suitable inhalation power in watts is determined for the INS electro-dose in step **150**.The activation pressure step **210** is set with respect to Figure 7 where the optimum effect in the inhalation is in region **I** and in region **I** the inhalation power is also at a maximum and the de-agglomeration of the electro-dose will be optimal. The time when the activation pressure is reached is at $t = t_s$ according to Figure 8 and at activation flow rate **20**.

After the preparation of the DPI at step 110 the respective inhaler is set to analysis 1 step **120** to determine if the settings are in accordance with the intended specification.

All measurements are made according to USP and a set-up according to Figure 1 is used to measure the uniformity of dose and the dose de-agglomeration DD3μm.

Results from analysis step 120

DPI A			
Inhalation flow	40	liters/minute	OK
Inhalation pressure	1.6	kPa	OK
Activation pressure	0.5	kPa	OK
Dose delivery time ts	0.5	s	OK
Dose delivery time Ts	2.1	s	OK
Activation time DPI T – t	3.1	s	OK
Closing pressure	1.0	kPa	OK
Electrical connection	yes		OK
DPI B			
Inhalation flow	40	liters/minute	OK
Inhalation pressure	2.6	kPa	OK
Activation pressure	0.5	kPa	OK
Dose delivery time ts	0.5	s	OK
Dose delivery time Ts	2.1	s	OK
Activation time DPI T – t	3.1	s	OK
Closing pressure	0.7	kPa	OK
Electrical connection	yes		OK

All pressures are measured in the same way as the pressure drop over the DPI **8** described in the USP together with a chronograph to measure the time intervals during the activation time DPI step **250**.

Analysis 1 in step **120** shows approved results and both DPI A and DPI B are approved for further tests and meet at step **140** the requirements for a prepared DPI.

An electro-dose step **150** of INS is now introduced and inserted into the respective DPI for further tests at step **160**.

A set of tests at different pressures according to Figure 20 are defined and performed where the de-agglomeration is measured and the point where the de-agglomeration is changing drastically as in transition region **II** and region **III** with the pressure identified. Analyses are performed in accordance with USP and in a set up according to figure 1 and measured using a HPLC.

As can be see in Figure 20 the DPI A is showing a worse behavior in region **II** compared with DPI B. If possible with respect to user comfort region **40** according to Figure 10 and behavior inside the comfort area according to Figure 11 the DPI B is a safer setting but the DPI A is having a higher performance inside region **I**.

Regarding dose retention 88 Figure 21 shows the need to optimize the DPI to be used into region **II**.

A report for determining approved Y/N step **180** is prepared giving the results of analysis 2.

Pressure drop kPa	De-agglomeration DD5µm %		Retention %	
	DPI A	DPI B	DPI A	DPI B
0.5	22	27	5	5
1	57	52	4	5
1.5	59	57	3	4
2	62	59	3	3
2.5	63	60	4	3
3	64	61	5	5
3.5	66	62	6	5
4	67	62	7	6

DPI A

Inhalation flow	40	liters/minute	OK
Inhalation pressure	1.6	kPa	OK
Activation pressure	0.5	kPa	OK
Dose delivery time ta	0.5	s	OK
Dose delivery time Ta	2.1	s	OK
Activation time DPI T – t	3.1	s	OK
Closing pressure	1.0	kPa	OK
Electrical connection	yes		OK
DD3µm	59	%	OK
Retention	3	%	OK

DPI B			
Inhalation flow	40	liters/minute	OK
Inhalation pressure	2.6	kPa	OK
Activation pressure	0.5	kPa	OK
Dose delivery time t_s	0.5	s	OK
Dose delivery time T_s	2.1	s	OK
Activation time DPI T – t	3.1	s	OK
Closing pressure	0.7	kPa	OK
Electrical connection	yes		OK
DD3μm	60	%	OK
Retention	3	%	OK

To verify if the DPI conforms to the specification of an EDPI the following calculations must be made.

	EDPI	DPI A	DPI B
DD3μm	> 25 %	59 %	60 %
Dose	1 μg - 10 mg	800 μg	800 μg
ΔDD3μm	< 50 %	12 %	16 %
Uniformity of dose	according to USP	Approved	Approved

Both DPI A and DPI B show approved results and are suitable for systemic delivery of INS 800 μg as EDPI inhalers for INS 800 μg. To determine if DPI A or DPI B is going to be decided for, further tests have to be performed by utilizing both analysis 1 in step **120** and analysis 2 in step **170** together and with users determining what inhalation pressure and flow they prefer to be inside a comfort area step **40**. It may also be considered that the de-agglomeration of the powder is too poor and further optimization of the deep lung delivery performance of DPI A and DPI B must be performed together with an optimization of the electro-dose step **150** of INS.

CLAIMS

1. A method for optimizing an electrostatically dosed dry powder inhaler (EDPI) for utilization of a prepared pre-metered electro-dose consisting of a electro-powder, **characterized by** the steps of

arranging a measurement set-up for measurement of parameters affecting a systemic delivery or local lung delivery of a pre-metered electro-dose from a dry powder inhaler, DPI, including analysis of dose de-agglomeration, particle size distribution as well as uniformity of dose together with pressures times and flows;

adjusting the DPI for a systemic or a local lung setting having a DPI with 20 to 60 liters per minute inhalation air flow for systemic delivery setting and 20 to 80 liters per minute for a local lung setting;

adjusting the desired de-agglomeration power between 0.1 and 6 watts to be used in the DPI by optimizing the pressure drop and inhalation flow rate;

adjusting the DPI activation pressure between 0.5 and 4 kPa to eliminate the low power at the start of an inhalation;

verifying that the DPI meets the specifications set regarding de-agglomeration power and opening pressure together with timings within the DPI active time;

verifying that a uniformity of dose meets regulatory demands;

verifying and optimizing a DPI not approved by adjusting the DPI and/or electro-dose to meet specifications of an EDPI.

2. The method according to claim 1, **characterized by** the further step of using an instrument for a physical particle size measurement in the measurement set up.

3. The method according to claim 1, **characterized by** the further step of verifying that de-agglomeration difference, expressed in percent using an expression 100[1-de-agglomeration(Q_{1kPa})/de-agglomeration(Q)], is not more

than 50%, where Q_{1kPa} represents a pressure drop over the inhaler device reduced to 1 kPa and Q representing a pressure drop according to USP.

4. The method according to claim 1, **characterized by** the further step of pre-defining the dose fine particle fraction of electro-powder particle size to be 3 μm or less for a systemic lung delivery of dose.

5. The method according to claim 1, **characterized by** the further step of pre-defining the aerodynamic mass median diameter of electro-powder particle size to be 5 μm or less for a localized lung delivery of dose.

6. The method according to claim 1, **characterized by** the further step of optimizing the de-agglomeration difference to less than 25 %.

7. The method according to claim 1, **characterized by** the further step of optimizing the de-agglomeration difference to less than 10 %.

8. The method according to claim 1, **characterized by** the further step of optimizing the uniformity of dose to meet 90 to 110 %.

9. The method according to claim 1, **characterized by** the further step of optimizing the uniformity of dose to meet 95 to 105 %.

10. The method according to claim 1, **characterized by** the further step of optimizing the dose de-agglomeration DD3μm for deep lung delivery to be more than 25 %.

11. The method according to claim 1, **characterized by** the further step of optimizing the dose de-agglomeration DD5μm for local lung delivery to be more than 25 %.

12. The method according to claim 1, **characterized by** the further step of optimizing the pressure drop over the mouthpiece and device member compared to the total pressure drop over the inhaler to be greater than 50 %.

13. The method according to claim 1, **characterized by** the further step of optimizing the dissipative connection between the user and the DPI to eliminate electrical fields due to potential differences.

14. The method according to claim 1, **characterized by** the further step of arranging a DPI closing pressure between 0,5 and 4 kPa to eliminate the low power at the end of the inhalation.

15 A method for controlling a dose delivery of a prepared pre-metered electro-dose, consisting of electro-powder, in relation to a time span for a user's full inspiration, by means of a dry powder inhaler, DPI, **characterized by** the steps of

arranging a necessary but not necessarily exclusive condition for starting of a dose delivery cycle, the condition being a set but adjustable minimum pressure drop across the DPI resulting from a user's inspiration through the DPI;

selecting a suitable starting point in time within the delivery cycle for dose delivery by adjusting a time delay as from the start of the cycle until the dose begins to be dispersed in inhalation air by a stream of air created inside the DPI and resulting from the user's inhalation;

adjusting a time span for dose delivery within the delivery cycle by adjusting the time during which the dose is dispersed by the stream of air created inside the DPI and resulting from the user's inhalation.

16. The method according to claim 15, **characterized by** the further step of adjusting the time span of dose delivery by adjusting a dose area, which a concentrated stream of air must cover in order to disperse an entire dose.

17. The method according to claim 15, **characterized by** the further step of adjusting the time span of dose delivery by varying a speed with which a concentrated stream of air moves relative to a dose area.

18. The method according to claim 15, **characterized by** the further step of controlling the amount of inhaled powder at every point in time during the dose delivery cycle by controlling amount of powder per unit area covered by the dose.

19. The method according to claim 15, **characterized by** the further step of controlling concentration of inhaled powder at every point in time during the dose delivery cycle by varying a speed with which the concentrated stream of air moves relative to the dose area.

20. A process for the delivery of a prepared pre-metered electro-dose, consisting of electro-powder, by means of a dry powder inhaler, DPI, **characterized in** that

an electro-dose presenting suitable pre-determined properties regarding total mass and physical distribution in three dimensions is formed as a dose area on a pre-determined target area of a device member;

a minimum pressure drop is defined between 0,5 and 4 kPa across the DPI, a necessary but not necessarily exclusive condition for triggering the dose delivery cycle;

a pre-determined timing is set for the delivery of the electro-dose within a total active time of an inhalation (t to T).

21. The process according to claim 20, **characterized in** that a time span of dose delivery is adjusted by adjusting a dose area, which a concentrated stream of air must cover in order to disperse an entire dose.

22. The process according to claim 20, **characterized in** that an amount of inhaled powder at every point in time during the dose delivery cycle is defined by the amount of powder per unit area covered by the dose.

23. The process according to claim 20, **characterized in** that concentration of inhaled powder at every point in time during the dose delivery cycle is defined by setting a speed with which a concentrated stream of air moves relative to the dose area.

24. A process for optimizing an electrostatically dosed dry powder inhaler (EDPI) for utilization of a prepared pre-metered electro-dose consisting of an electro-powder, **characterized by**

an arrangement of a measurement set-up for measuring parameters affecting a systemic delivery or local lung delivery of a pre-metered electro-dose from a DPI including analysis of dose de-agglomeration, particle size distribution as well as dose-to-dose variation together with pressures, times and flows;

an adjustment of the DPI for a systemic or a local lung setting having a DPI with a 20 to 60 liters per minute inhalation air flow for systemic delivery setting and 20 to 80 liters per minute for a local lung setting;

an adjustment of a desired de-agglomeration power between 0.1 and 6 watts to be used in the DPI by optimizing pressure drop and inhalation flow rate;

an adjustment of DPI activation pressure between 0,5 and 4 kPa to eliminate a low power at a start of an inhalation;

a verification that the DPI meets the set specification regarding de-agglomeration power and opening pressure together with timings within a DPI active time;

a verification that uniformity of dose meets regulatory demands;

a verification and optimization of a DPI not approved by adjustment of the DPI and/or electro-dose to meet specifications of an EDPI.

25. The process according to claim 24, **characterized by** utilization of an instrument for a physical size measurement in the measurement set-up.

26. The process according to claim 24, **characterized by** utilization of a verification that de-agglomeration difference, expressed in percent using an expression 100[1-de-agglomeration(Q_{1kPa})/de-agglomeration(Q)], is not more than 50%, where Q_{1kPa} represents a pressure drop over the inhaler device reduced to 1 kPa and Q representing a pressure drop according to USP.

27. The process according to claim 24, **characterized by** a pre-definition of the aerodynamic mass median diameter of electro-powder particle size to be 3 μm or less for a systemic delivery of dose.

28. The process according to claim 24, **characterized by** a pre-definition of the aerodynamic mass median diameter of electro-powder particle size to be 5 μm or less for a local delivery of dose.

29. The process according to claim 24, **characterized by** an optimization of the de-agglomeration difference to be less than 25 %.

30. The process according to claim 24, **characterized by** an optimization of the de-agglomeration difference to less than 10 %.

31. The process according to claim 24, **characterized by** an optimization of uniformity of dose to meet 90 to 110 %.

32. The process according to claim 24, **characterized by** an optimization of uniformity of dose to meet 95 to 105 %.

33. The process according to claim 24, **characterized by** an optimization of dose de-agglomeration DD3μm for deep lung delivery to be more than 25 %.

34. The process according to claim 24, **characterized by** an optimization of dose de-agglomeration DD5μm for local lung delivery to be more than 25 %.

35. The process according to claim 24, **characterized by** an optimization of pressure drop over the mouthpiece and device member compared to a total pressure drop over the DPI to be greater than 50 %.

36. The process according to claim 24, **characterized by** an optimization of the dissipative connection between a user and the DPI to eliminate electrical fields due to potential differences.

37. The process according to claim 24, **characterized by** an adjustment of extended dose delivery time in relation to a time for a user's full inspiration by an adjustment of a length of a powder strip on a dosing member to be used.

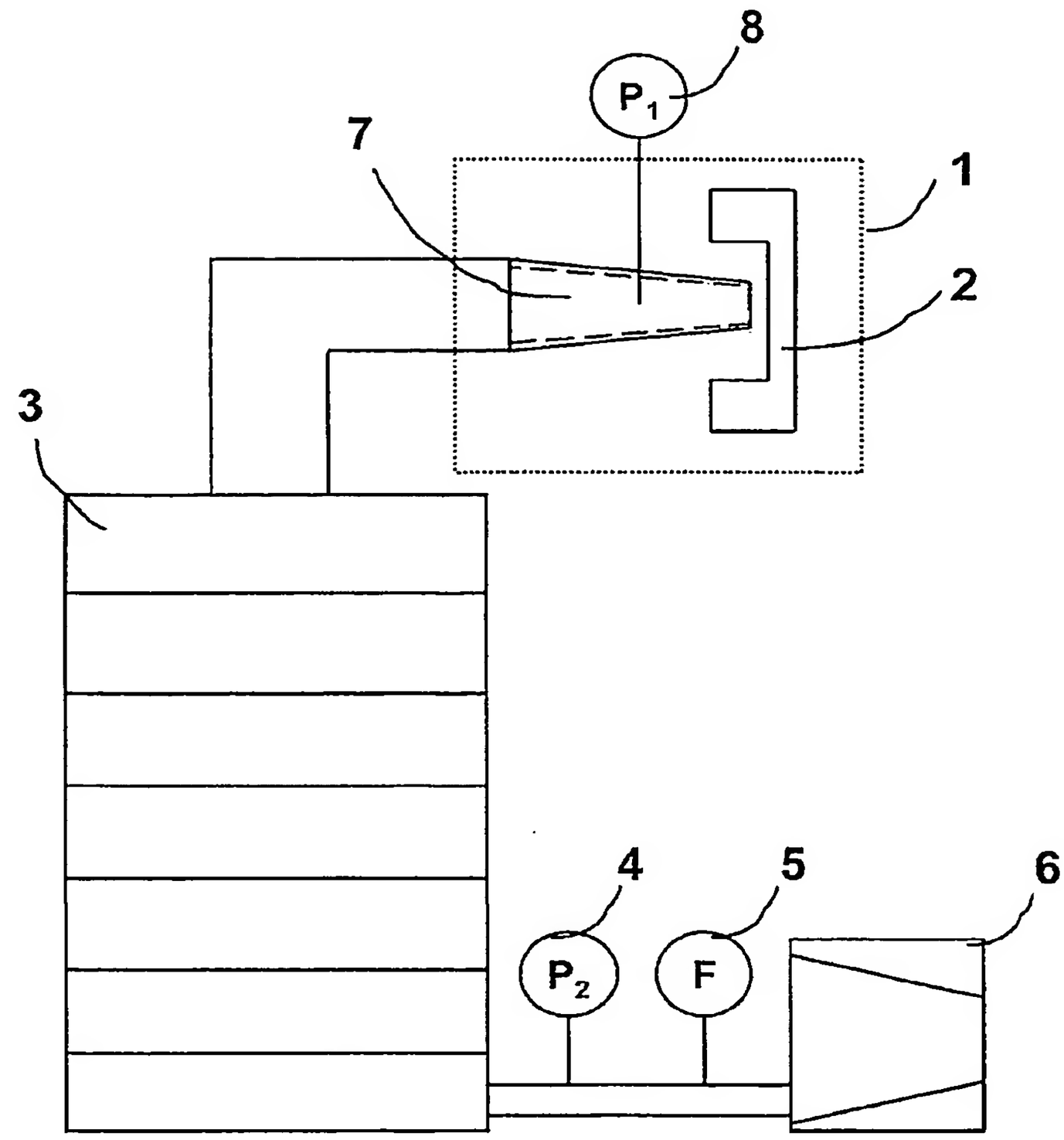

Fig. 1

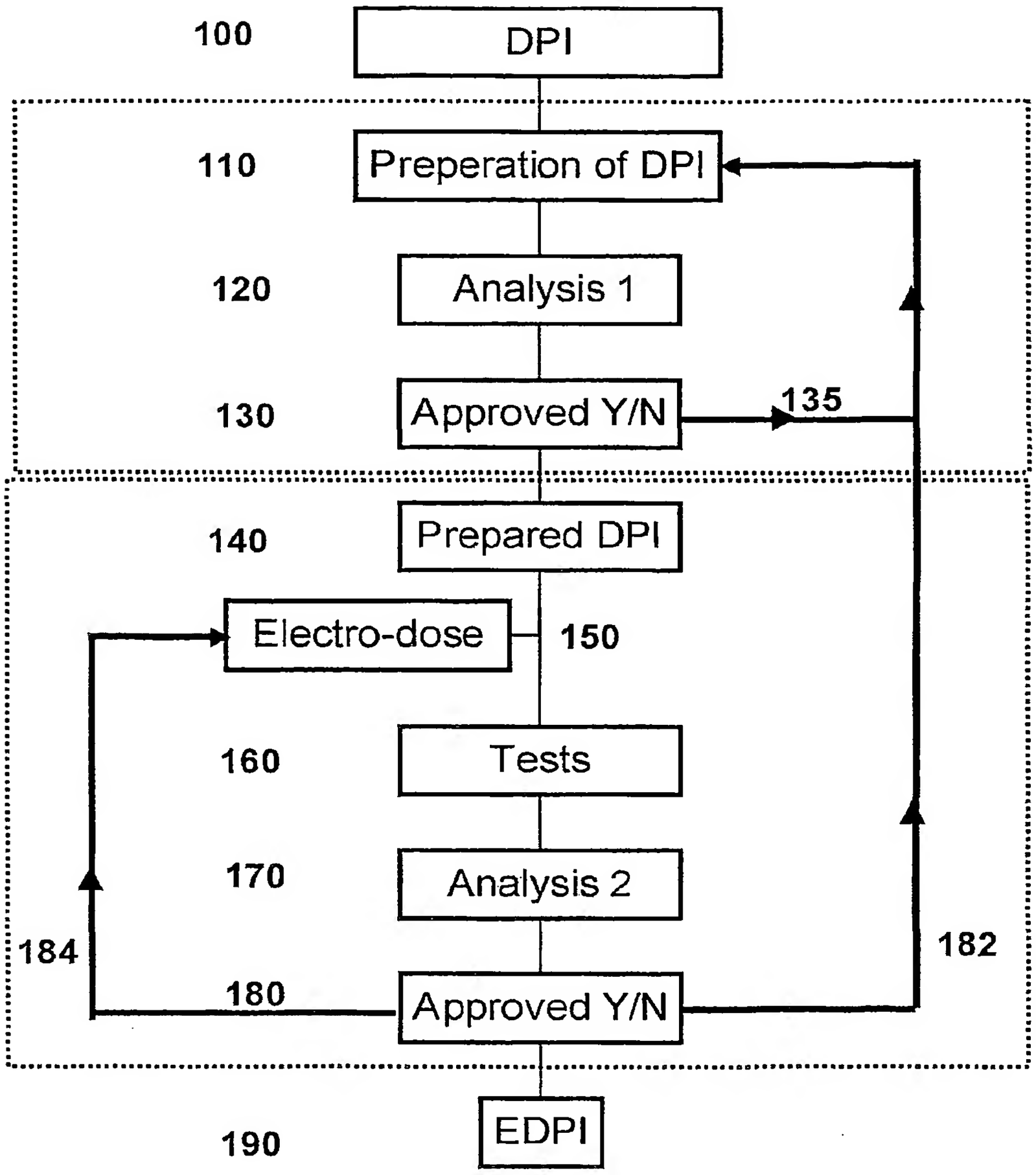

Fig. 2

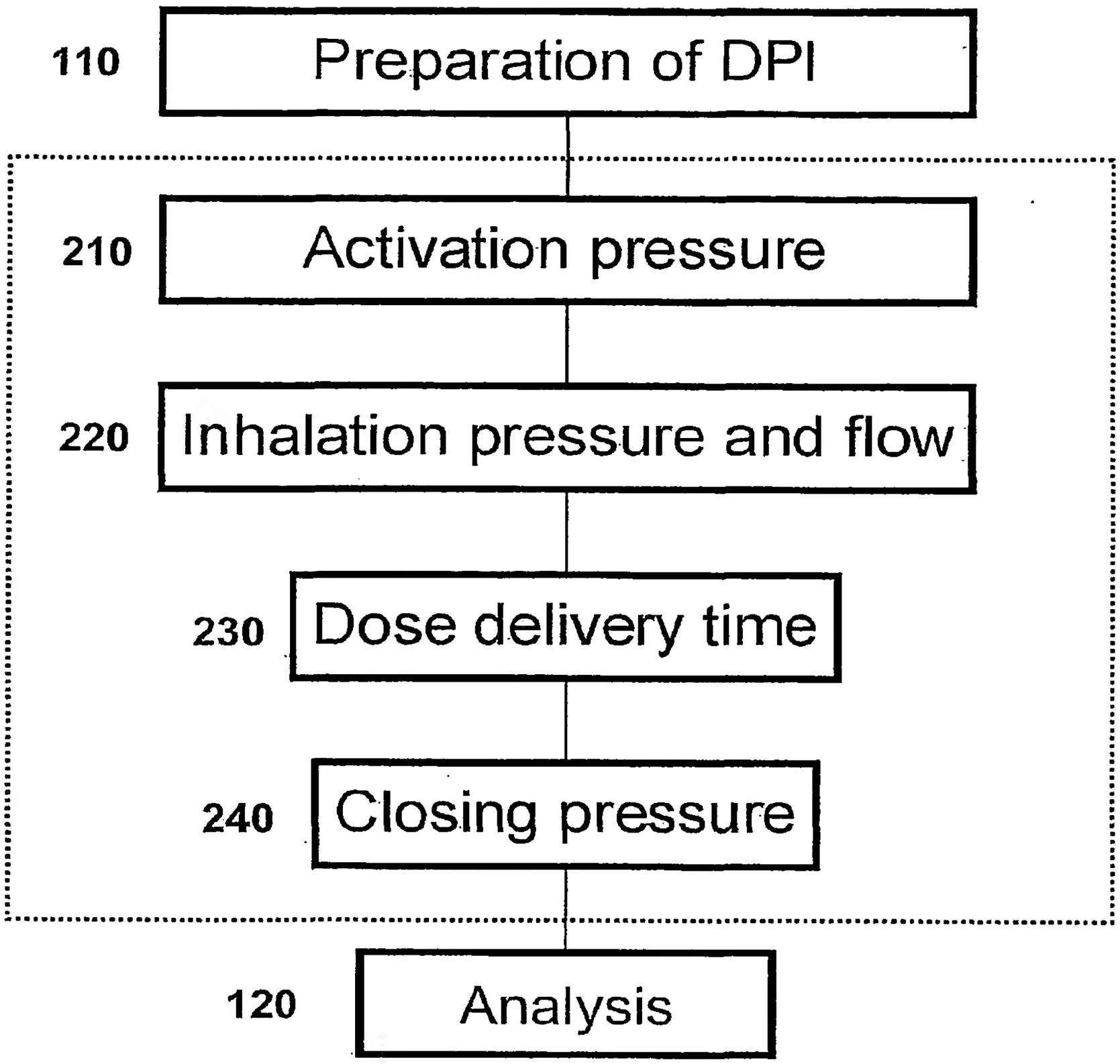

Fig. 3

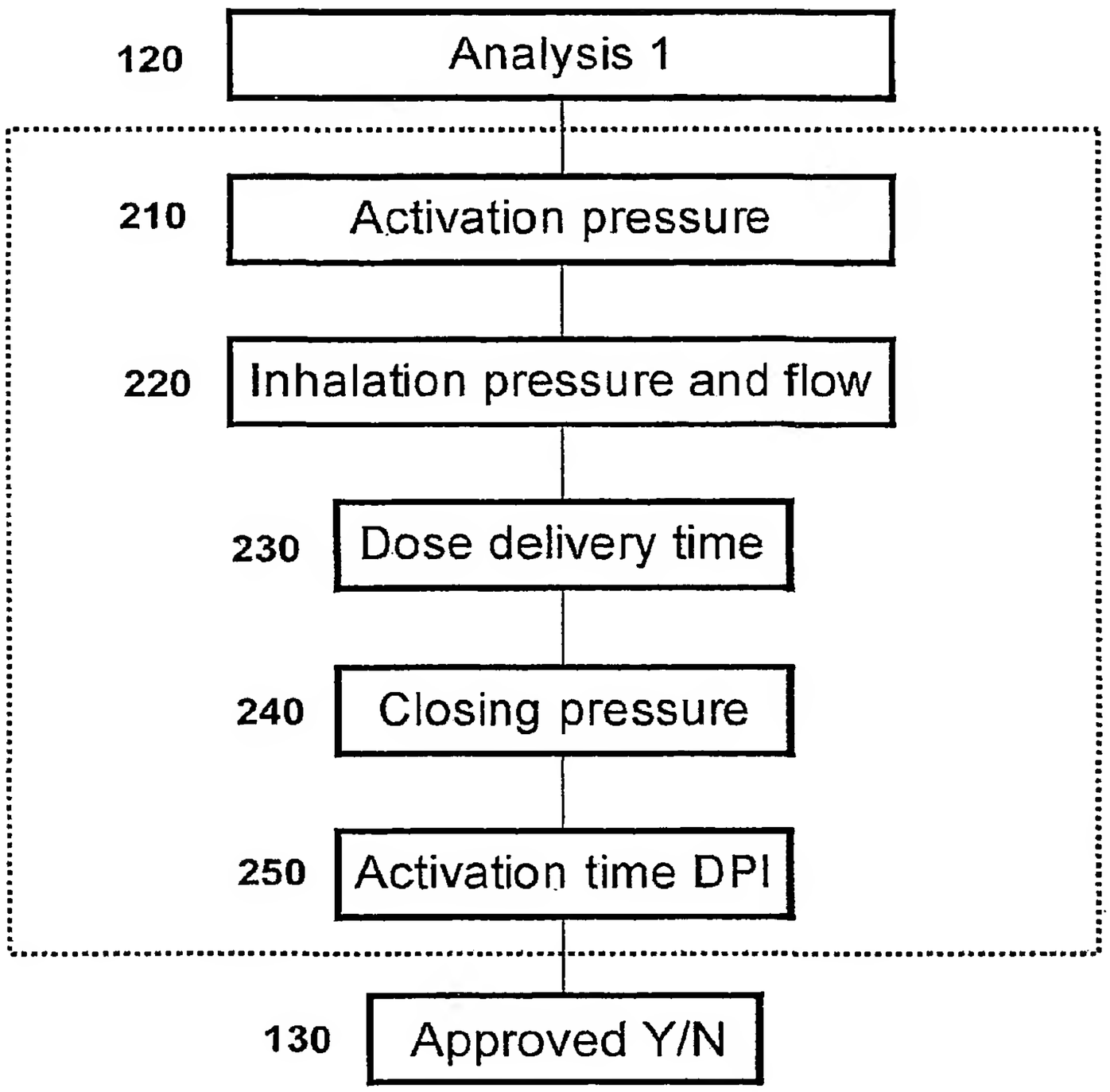

Fig. 4

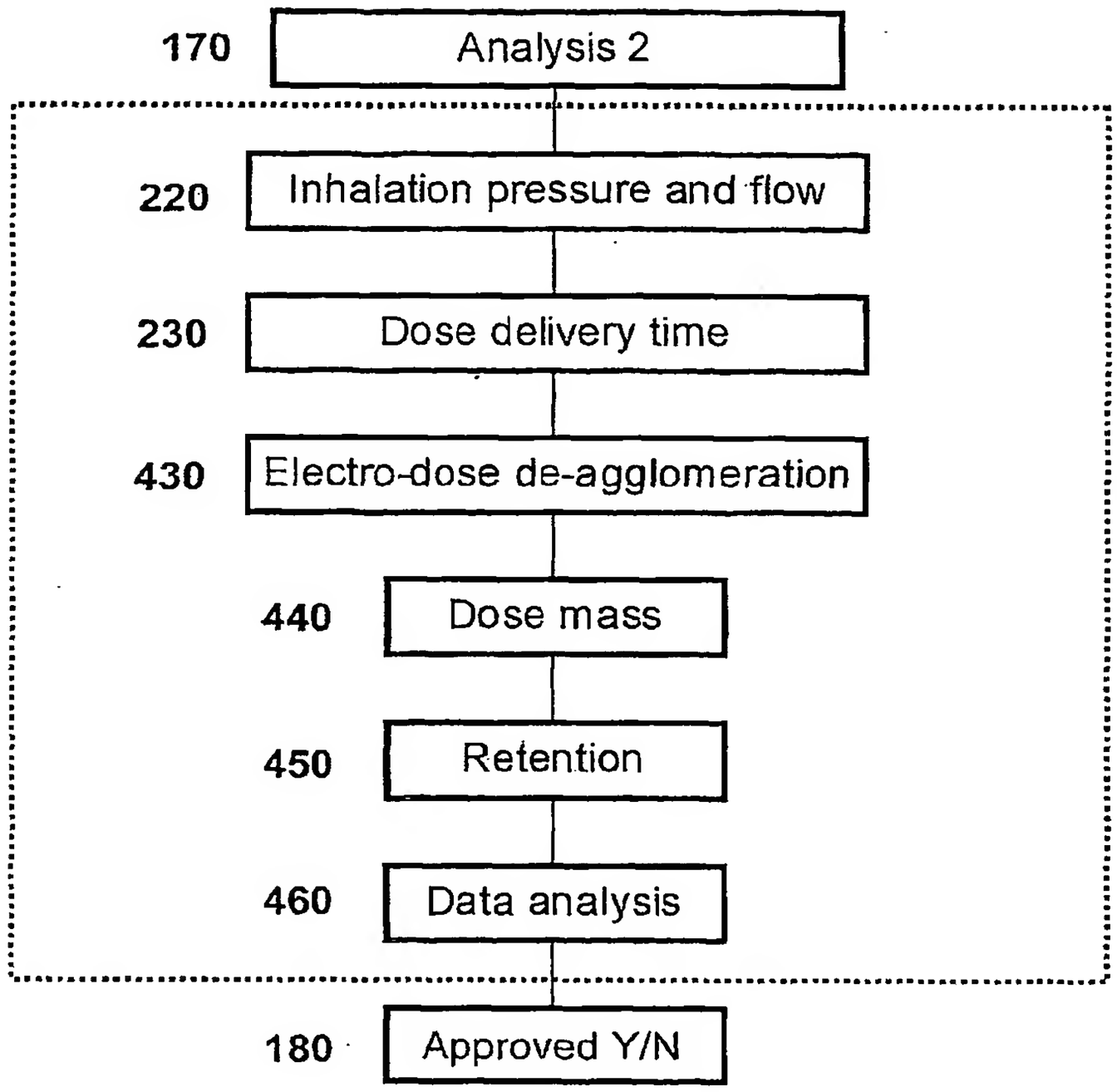
170
Analysis 2
220
Inhalation pressure and flow
230
Dose delivery time
430
Electro-dose de-agglomeration
440
Dose mass
450
Retention
460
Data analysis
180
Approved Y/N

Fig. 5

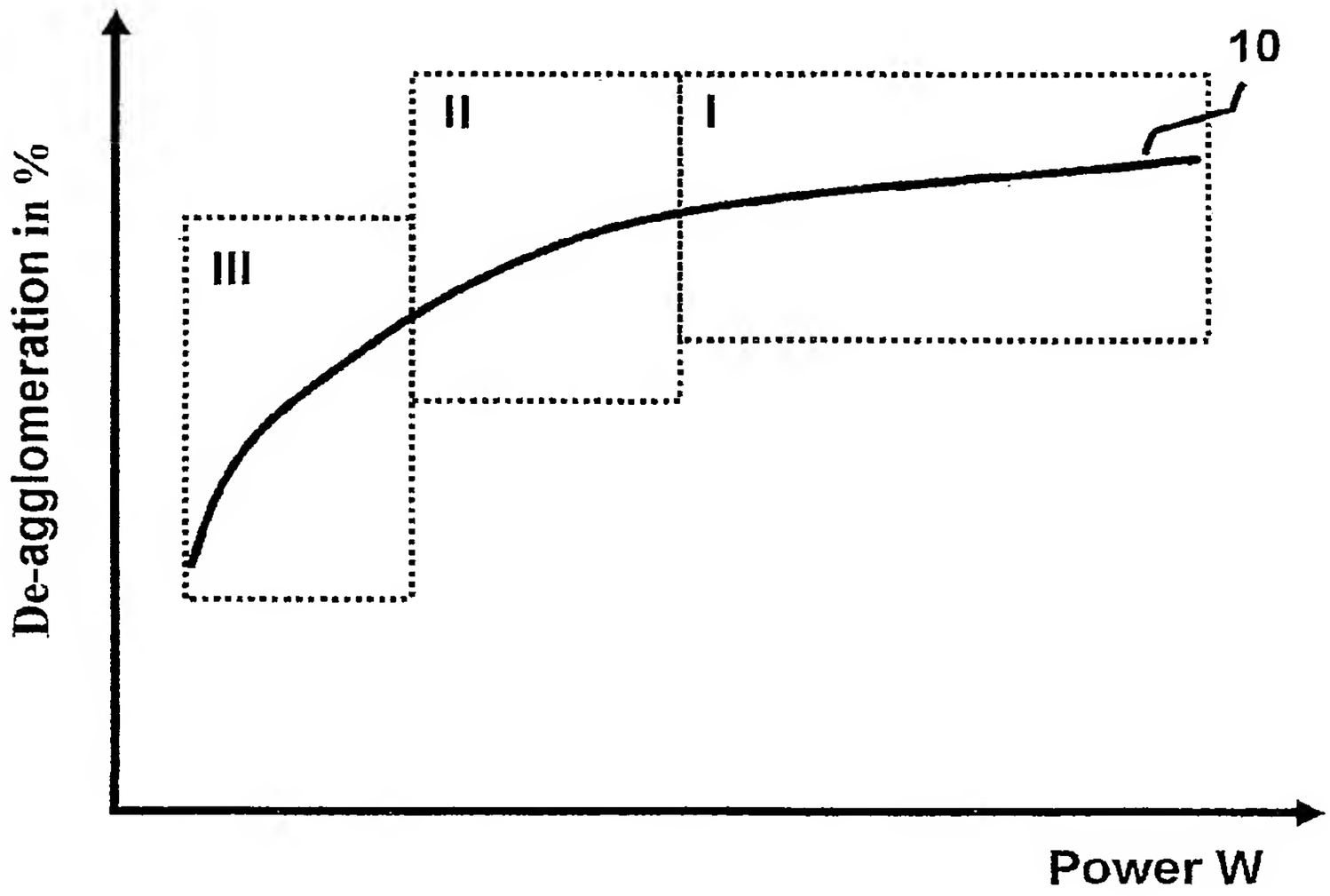

Fig. 6

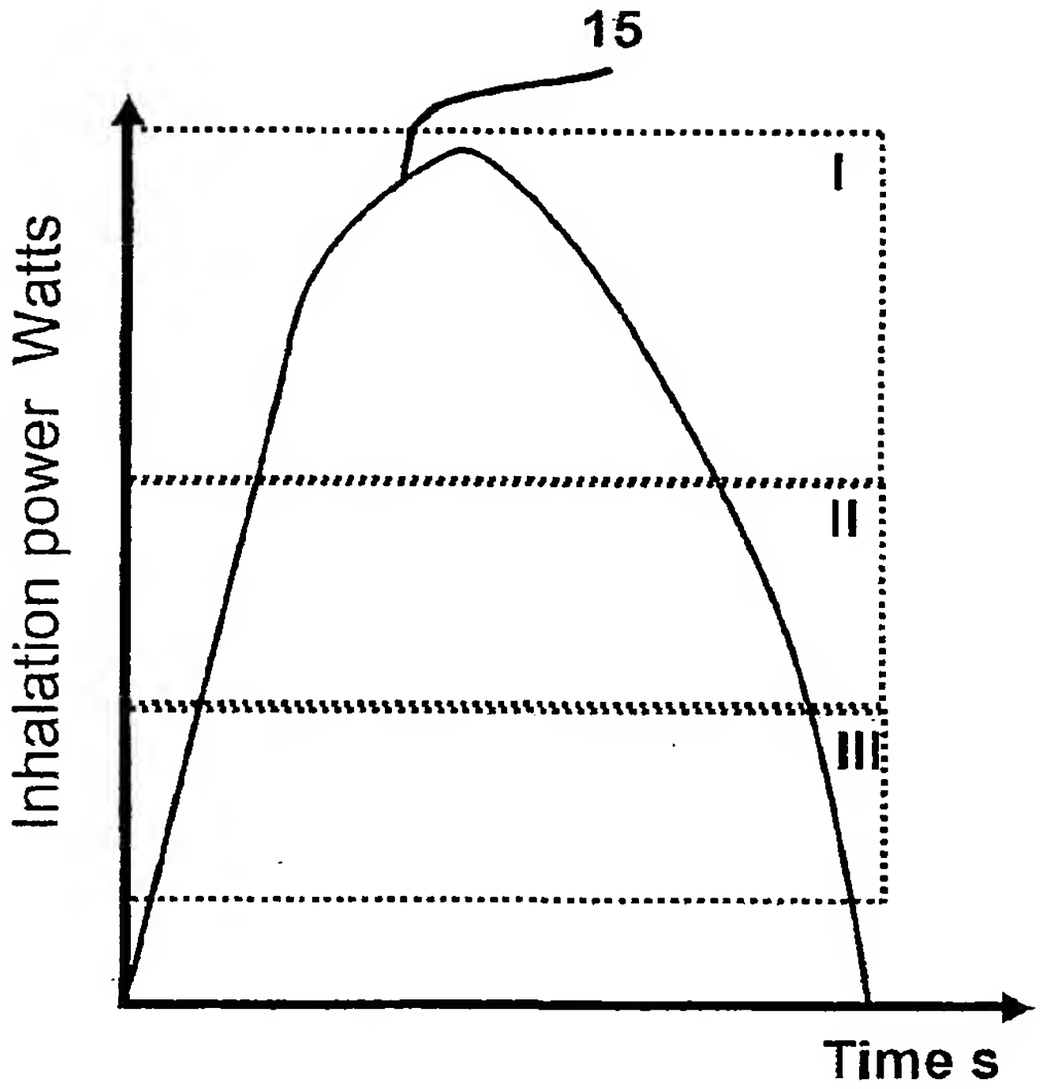

Fig. 7

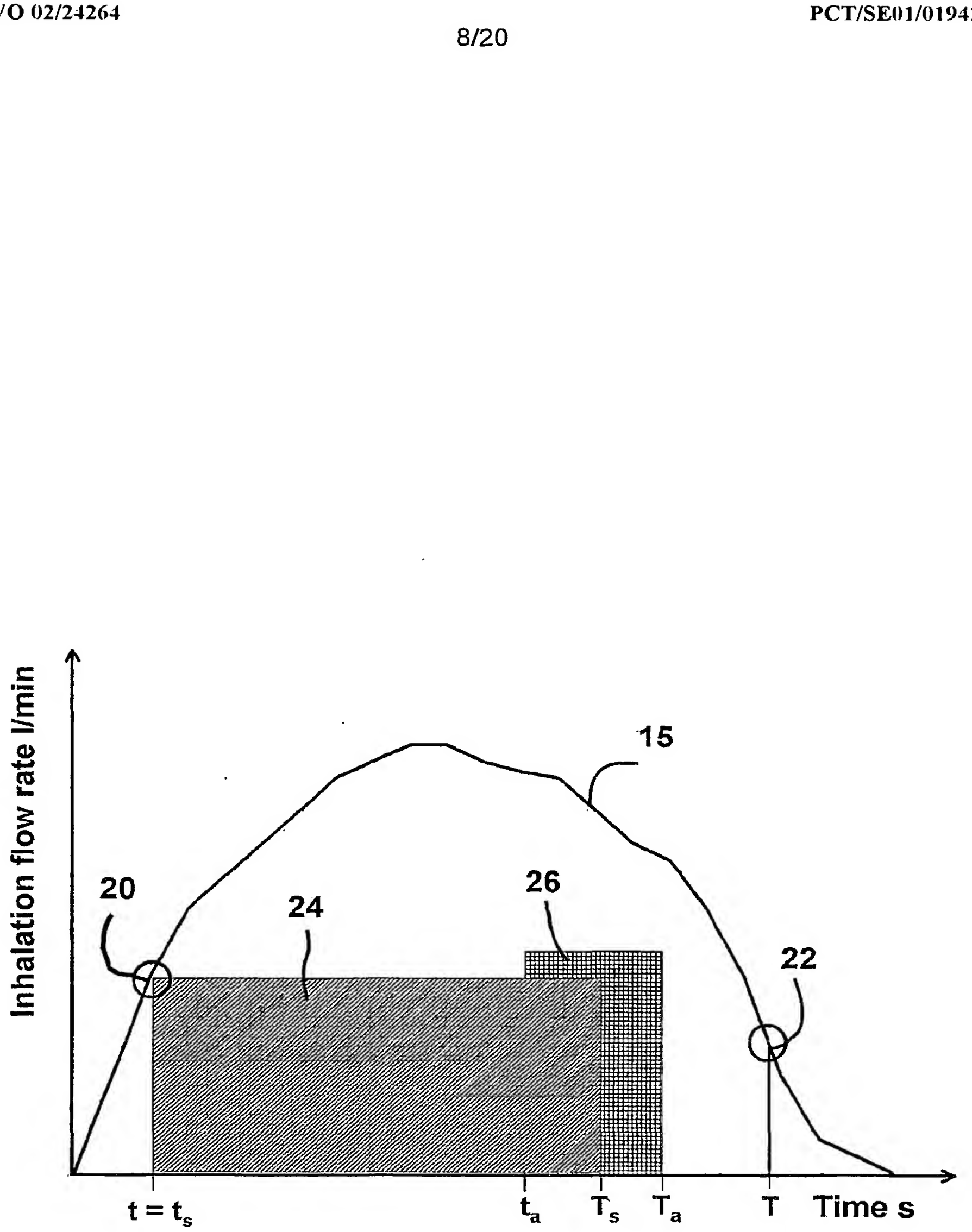

Fig. 8

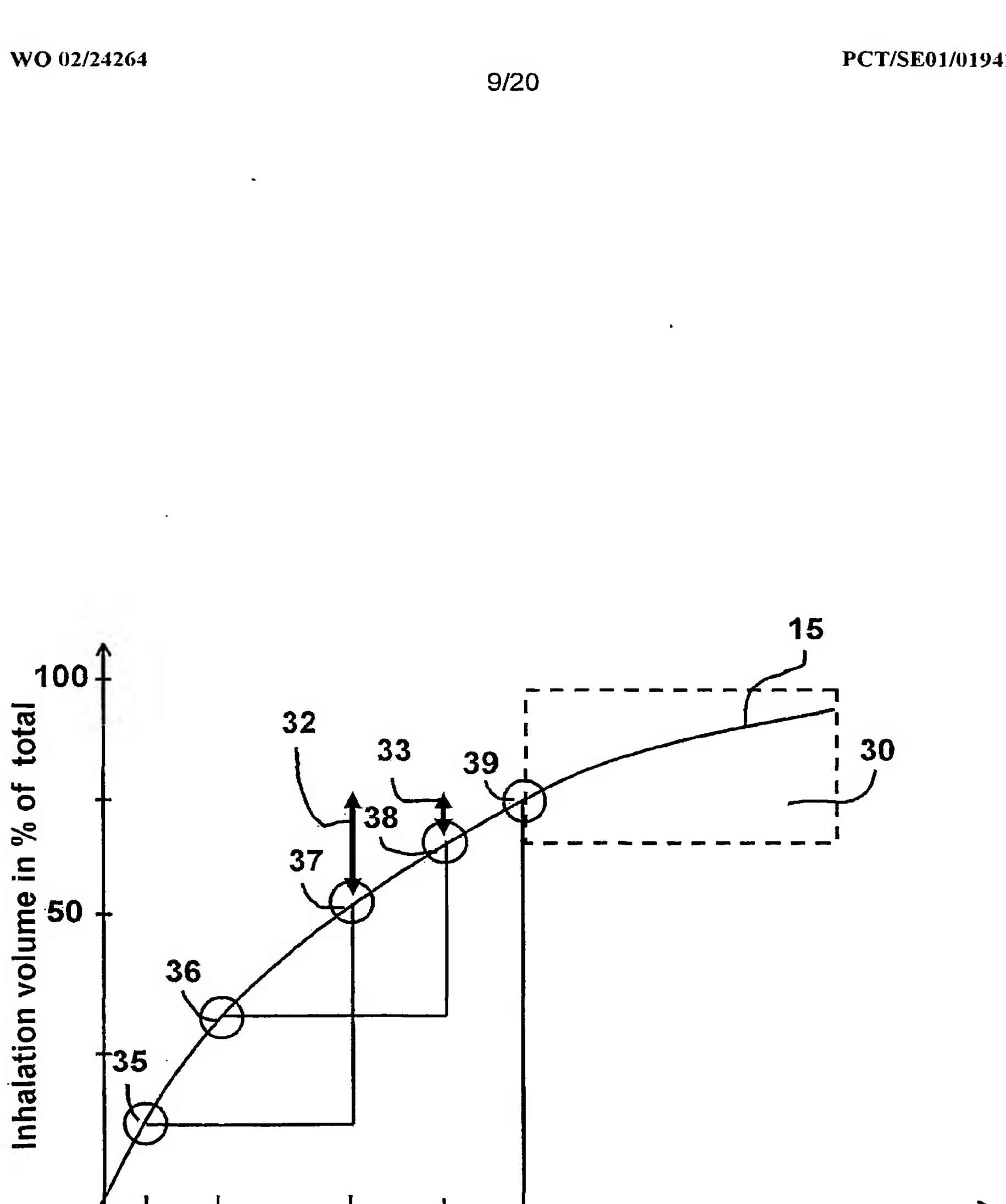
15
100
32
33
39
30
38
37
50
36
35
Inhalation volume in % of total
t = t_s
t_a
T_s
T_a
T
Time seconds

Fig. 9

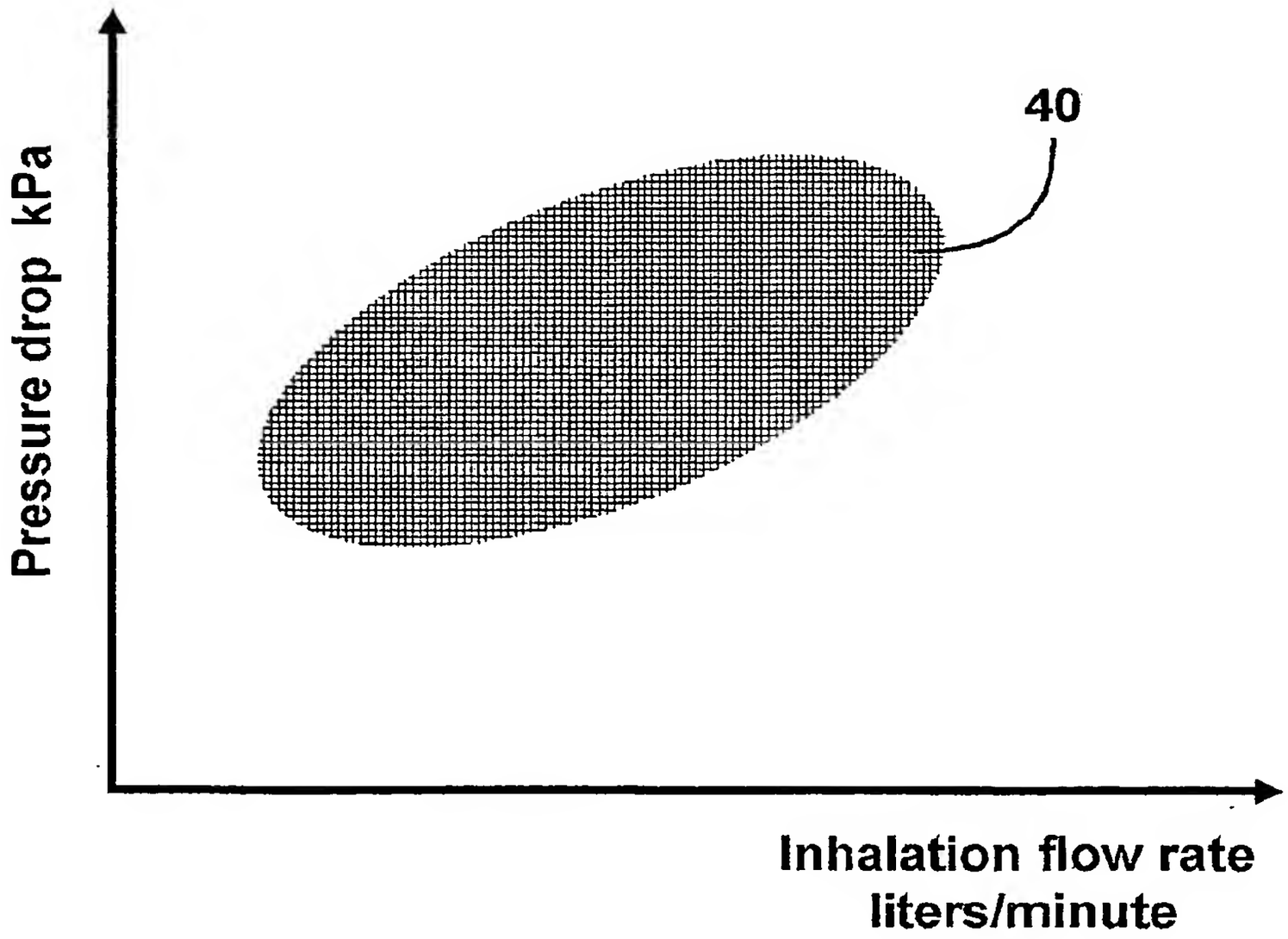

Fig. 10

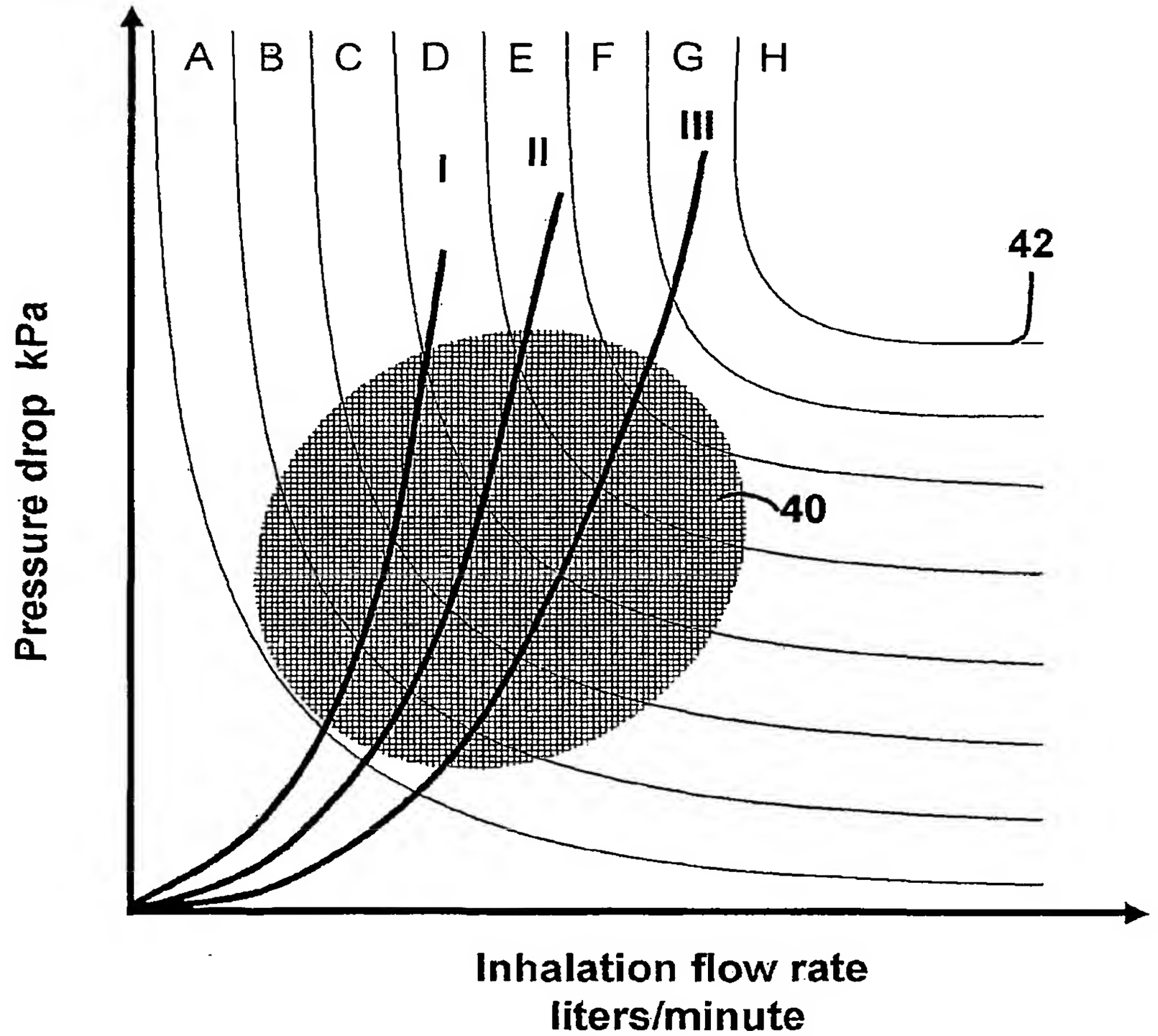
A
B
C
D
E
F
G
H
I
II
III
42
40
Pressure drop kPa
Inhalation flow rate
liters/minute

Fig. 11

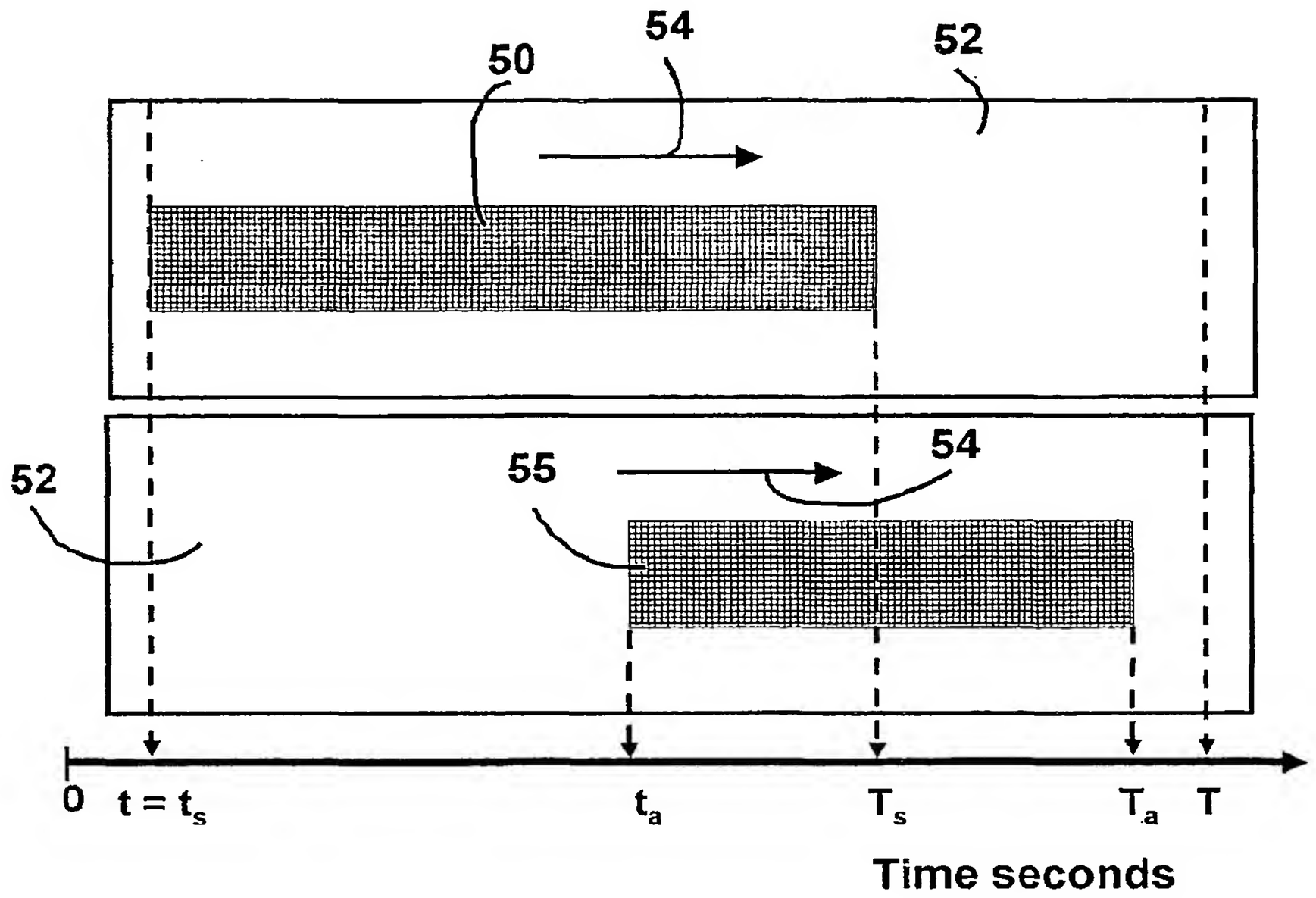

Fig. 12

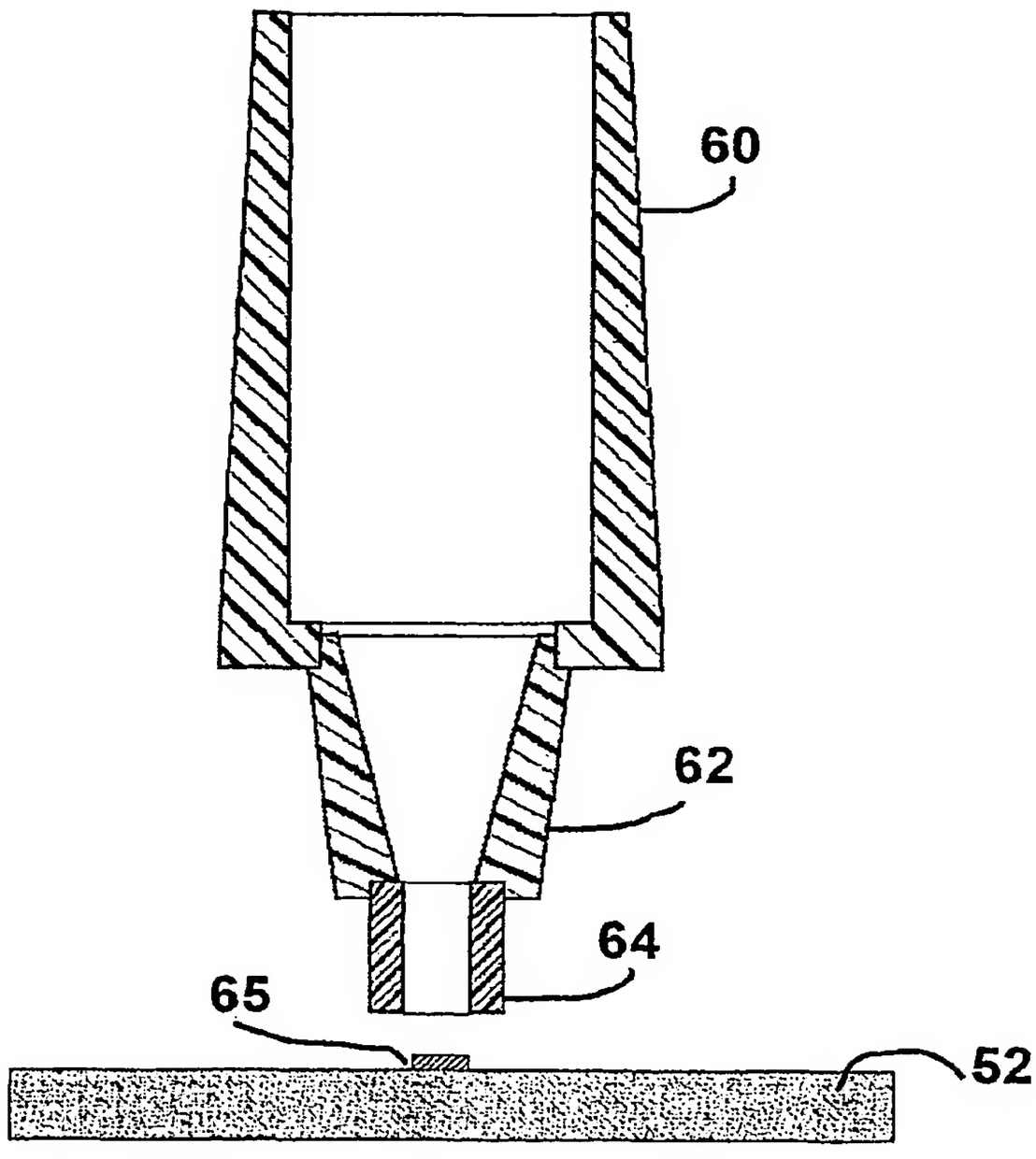

Fig. 13

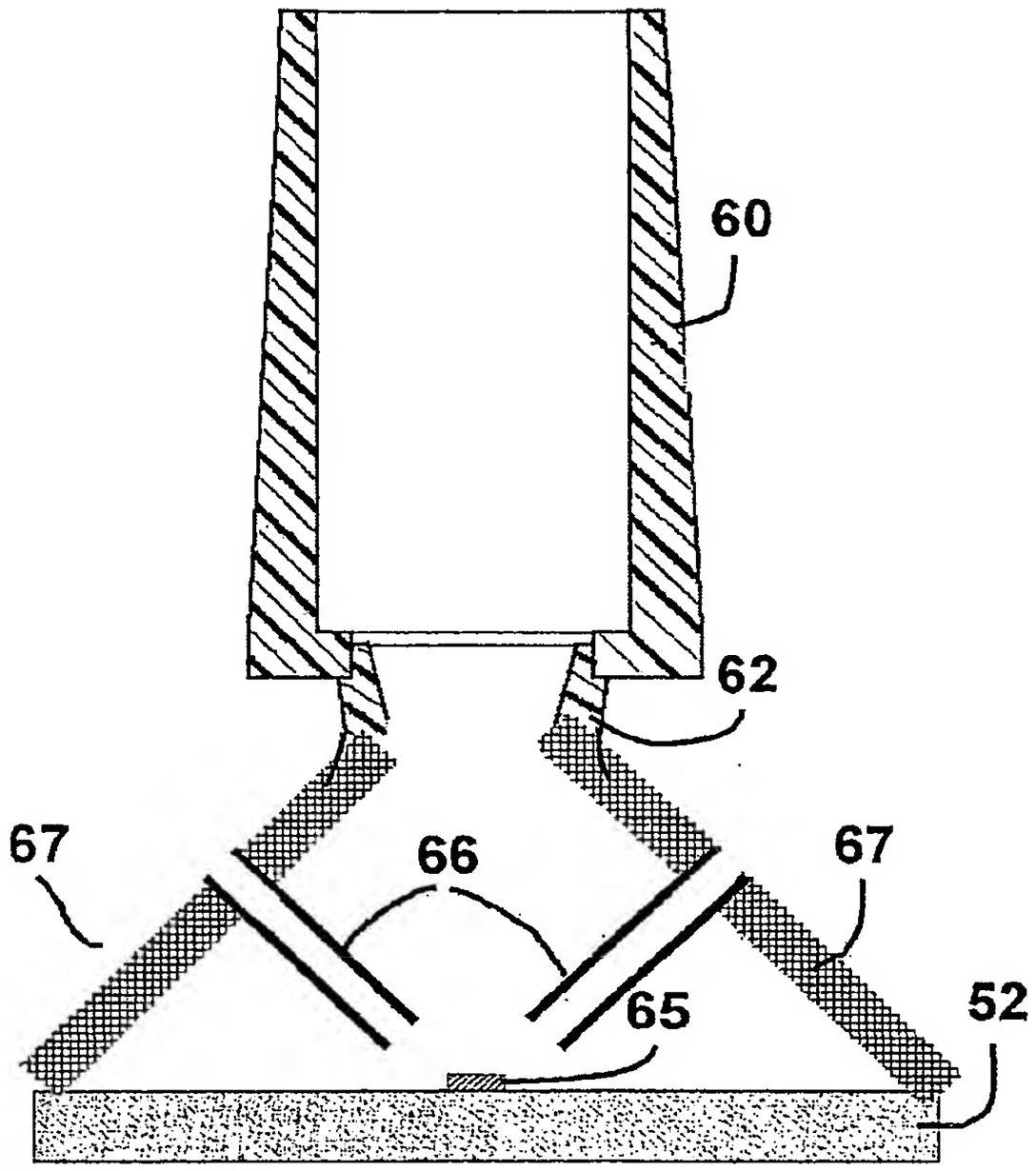

Fig. 14

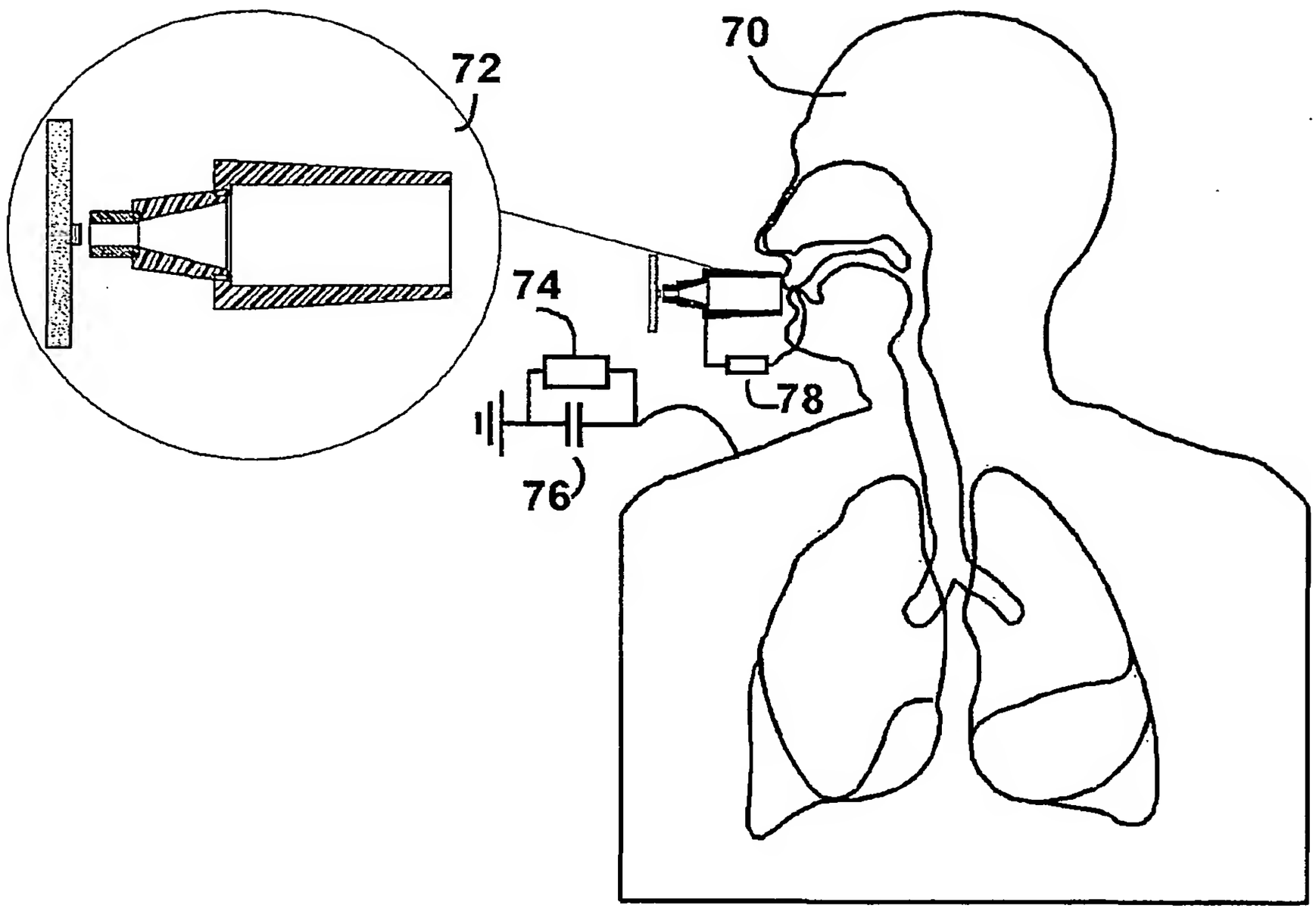

Fig 15

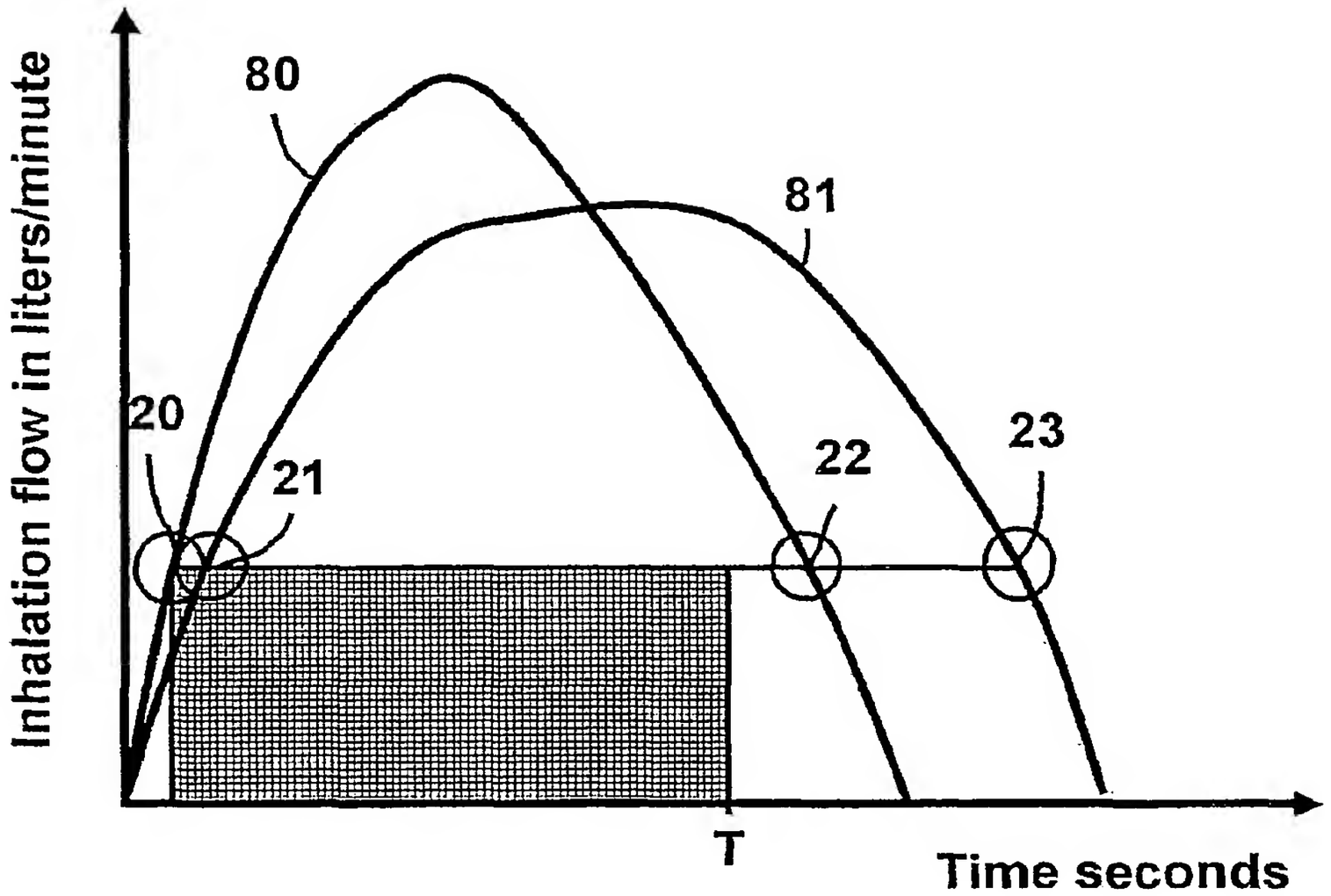
Inhalation flow in liters/minute
80
81
20
21
22
23
T
Time seconds

Fig. 16

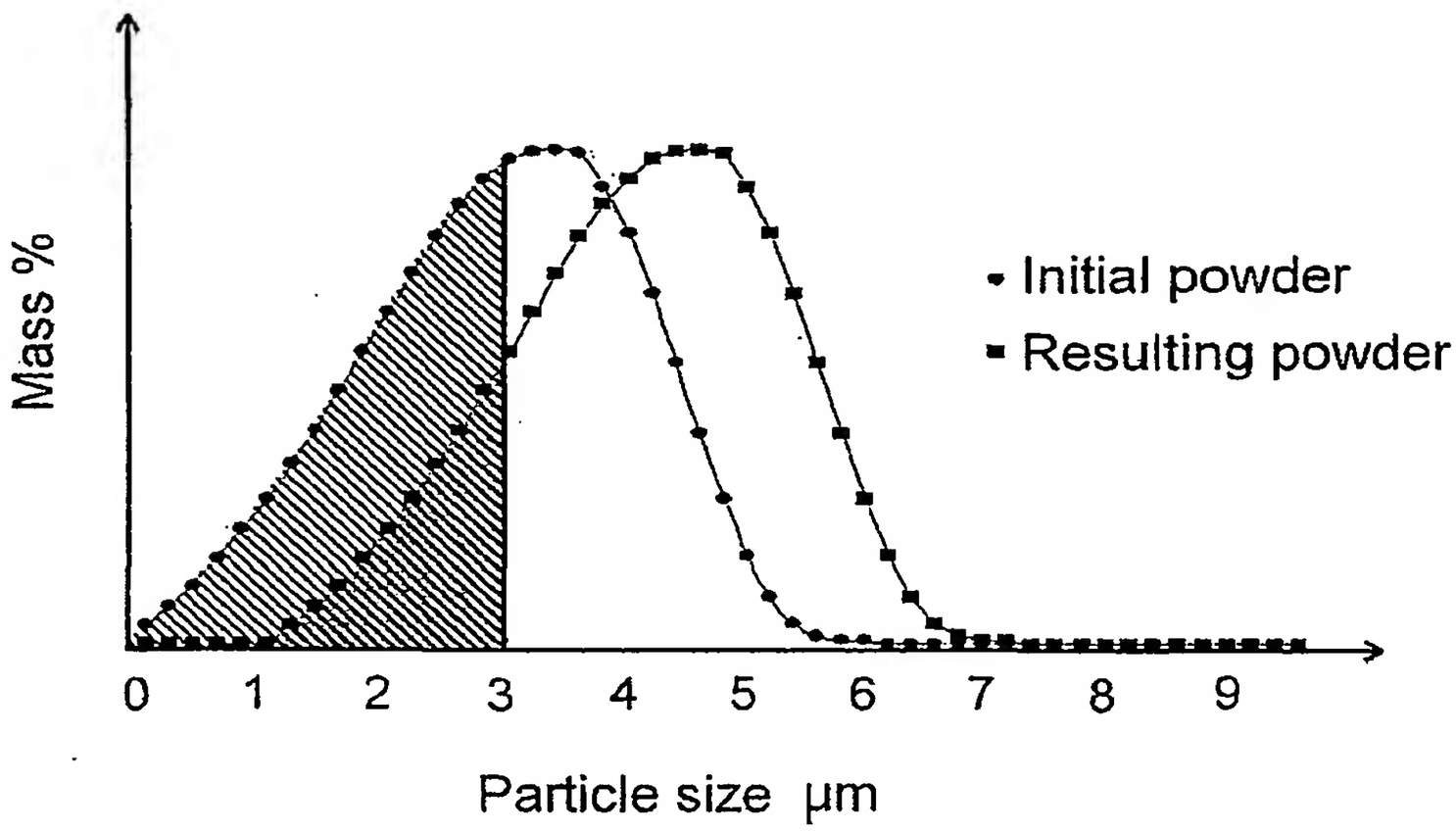
Mass %
Initial powder
Resulting powder
0 1 2 3 4 5 6 7 8 9
Particle size µm

Fig. 17

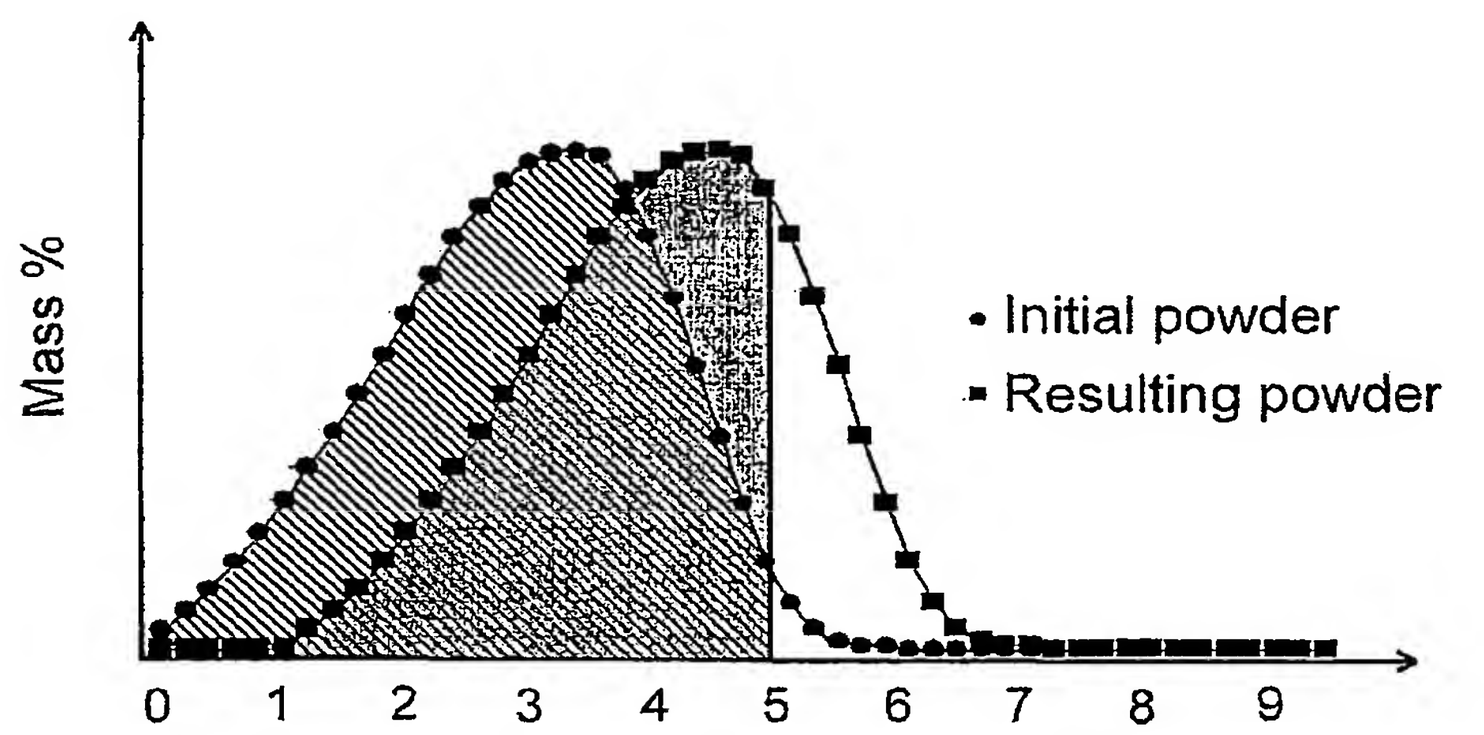
Mass %
Initial powder
Resulting powder
0 1 2 3 4 5 6 7 8 9
Particle size µm

Fig. 18

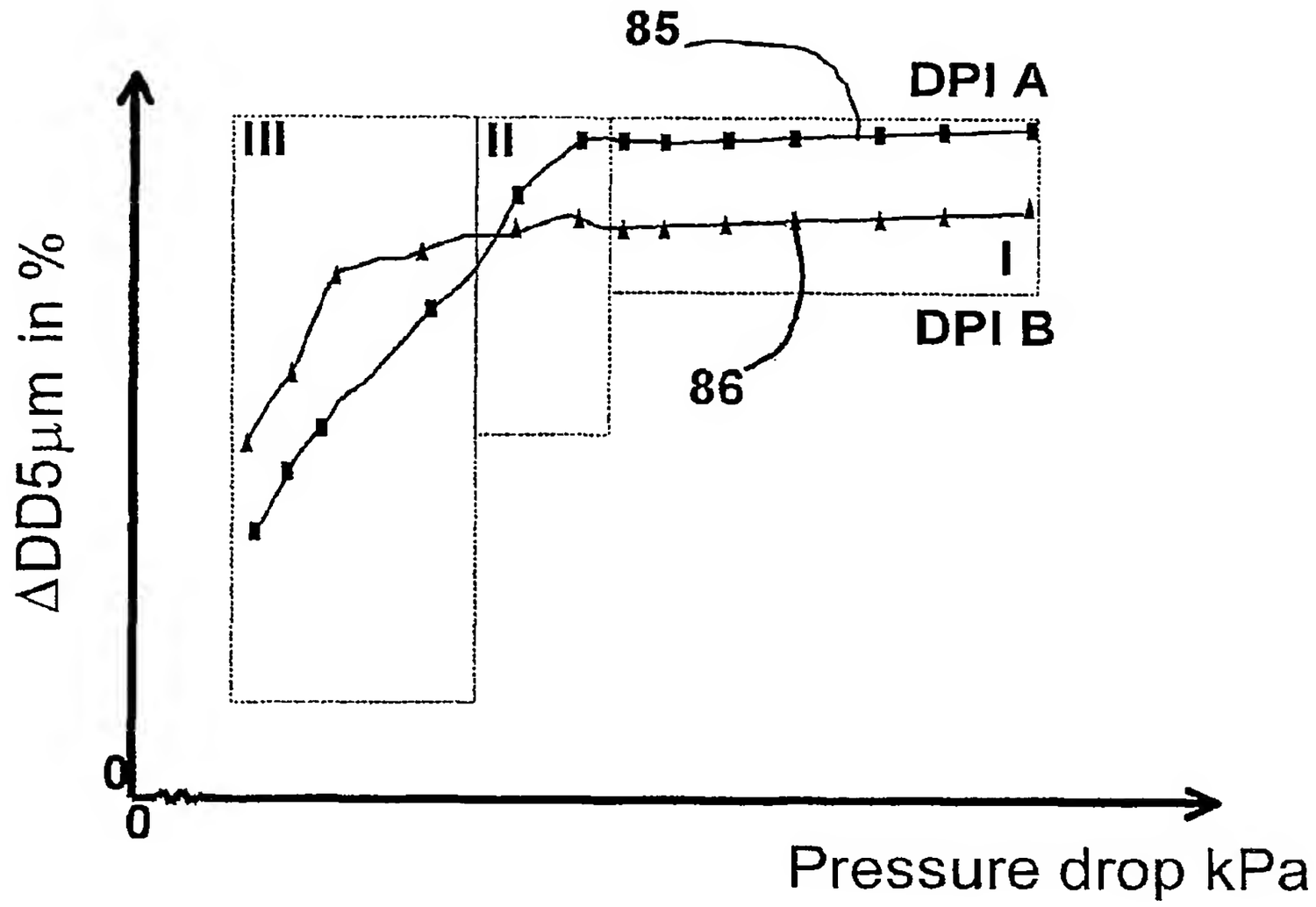

Fig. 19

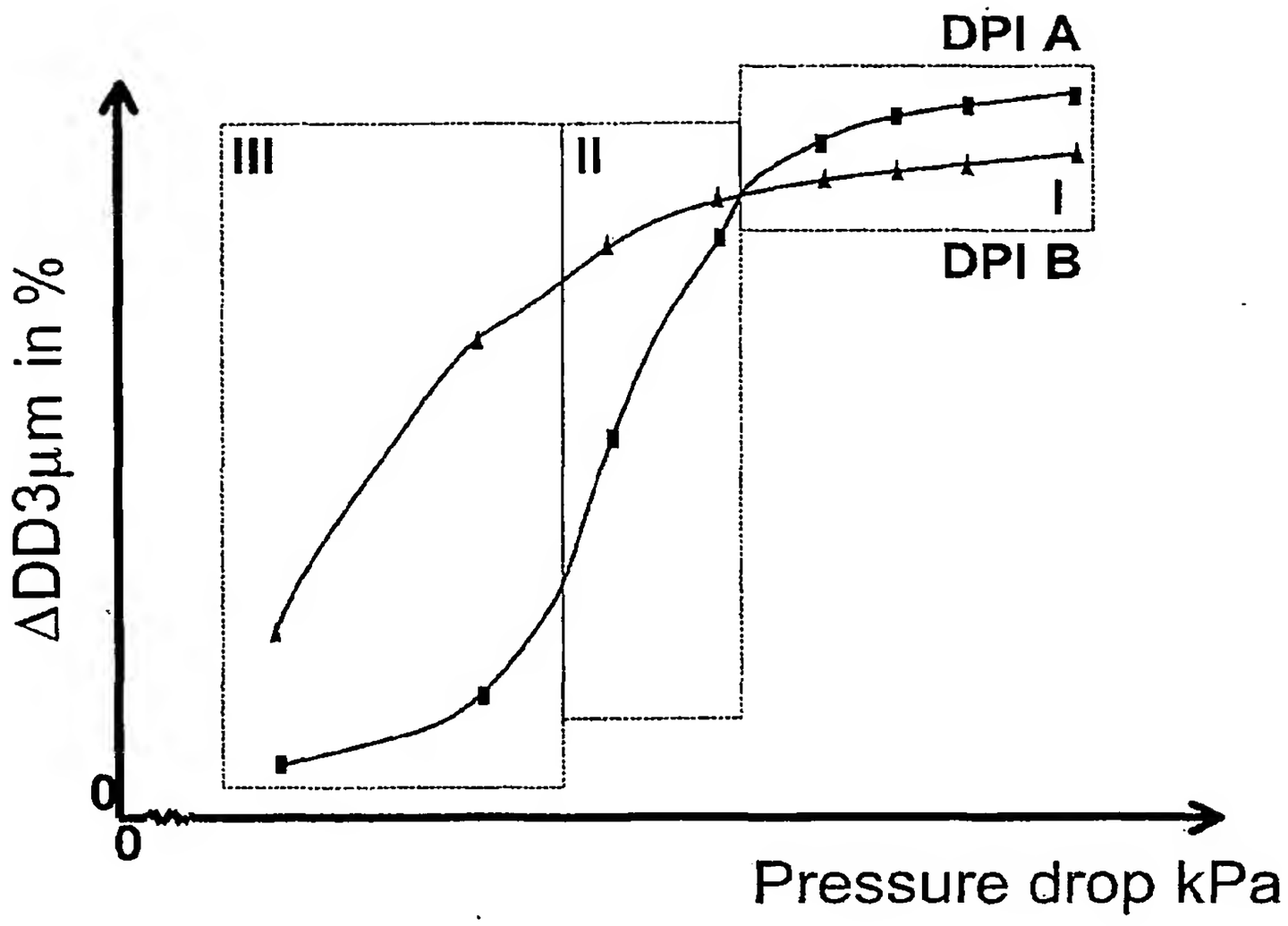

Fig. 20

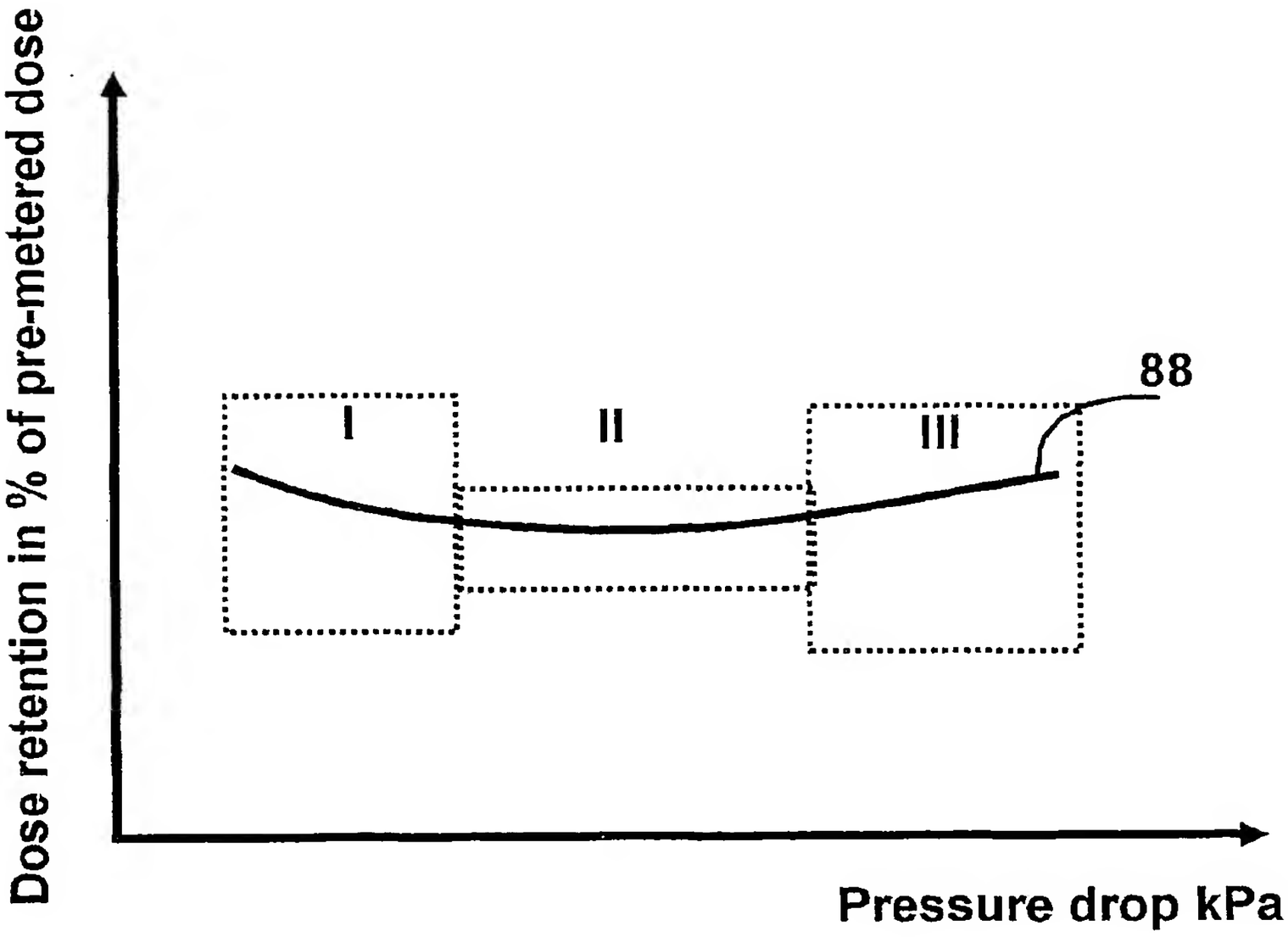
Dose retention in % of pre-metered dose
88
I
II
III
Pressure drop kPa

Fig. 21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/01942

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61M 15/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5694920 A (A L ABRAMS ET AL), 9 December 1997 (09.12.97), abstract, fig.	1-37
A	US 6142146 A (A L ABRAMS ET AL), 7 November 2000 (07.11.00), abstract, fig.	1-37
A	WO 9013327 A1 (RIKER LABORATORIES INC), 15 November 1990 (15.11.90), abstract, fig.	1-37
A	US 5819726 A (REID M RUBSAMEN ET AL), 13 October 1998 (13.10.98), abstract, fig.	1-37

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 January 2002	26-01-2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Hélène Erikson/JAn Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/01942

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6055979 A (FUCHS), 2 May 2000 (02.05.00), abstract, fig. --	15-23
A	US 4558710 A (EICHLER), 17 December 1985 (17.12.85), abstract, fig. --	15-23
A	GB 2164569 A (ETELA-HAMEEN KEUHKOVAMMAYHDISTYS RY), 26 March 1986 (26.03.86), abstract, fig. --	15-23

INTERNATIONAL SEARCH REPORT

Information on patent family members

27/12/02

International application No.
PCT/SE 01/01942

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US 6026809 A	22/02/00
		WO 9726934 A	31/07/97
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		WO 9832479 A	30/07/98
US 6142146 A	07/11/00	AU 3401597 A	07/01/98
		AU 4683199 A	30/12/99
		CN 1320054 T	31/10/01
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		EP 1083952 A	21/03/01
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		DK 472598 T	29/07/96
		EP 0470154 A,B	12/02/92
		SE 0470154 T3	
		EP 0472598 A,B	04/03/92
		SE 0472598 T3	
		EP 0705614 A	10/04/96
		ES 2087911 T	01/08/96
		ES 2091825 T	16/11/96
		GB 8909891 D	00/00/00
		GB 9000261 D	00/00/00
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		JP 3130925 B	31/01/01
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INTERNATIONAL SEARCH REPORT

Information on patent family members

27/12/02

International application No.
PCT/SE 01/01942

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		DE 3174689 D	00/00/00
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		FI 76929 B,C	30/09/88
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		GB 8519075 D	00/00/00
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		SU 1679968 A	23/09/91